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THE ELECTROCARDIOGRAM IN HYPERTENSION[1]

By A. W. D. LEISHMAN

(From the Royal Infirmary, Sheffield)

With Plates 1 to 6

Every physician attempts to assess the prospects of his hypertensive patients, and in this he is largely influenced by the extent to which vital functions are impaired as a result of the hypertensive condition. The electrocardiogram is included as an essential part of the investigation, and is recorded as normal or abnormal, but in the present state of our knowledge there is little justification for saying more than this. The expression 'patterns of left ventricular strain' satisfies no one, least of all the physicians who resort to it, and the real significance of the abnormal electrocardiogram associated with hypertension remains highly speculative. The physician is at a disadvantage in not knowing how much his prognosis should be influenced by an abnormal electrocardiogram. The author's experience of a large group of hypertensive patients has served only to accentuate this uncertainty, but a record of his observations was thought to be justified on the ground that the relevant facts are not widely known. The present study has been based on a series of 218 hypertensive patients from a group whose progress is being observed at a special clinic, with full investigation at regular intervals. All the patients in this series are below 60 years of age, and have a diastolic blood-pressure of 100 mm. Hg or more; no other criteria have been used in selecting them.

Electrocardiograms

At first electrocardiograms were recorded with the three standard leads and two chest leads, CF_4 and CF_5; subsequently all the augmented unipolar leads have been employed. An analysis of the 218 electrocardiograms is shown in Table I; 105 were judged to be normal, 86 showed major abnormalities, including inversion of T waves, and 27 showed certain other minor abnormalities. T-wave inversion in hypertensive electrocardiograms is commonly associated with depression (never elevation) of the ST segments; Q waves are not seen, and both these points distinguish the pattern from that of myocardial infarct, at least of recent origin. On occasions, however, it may be difficult, if not impossible, to exclude the possibility that the electrocardiographic changes are due to stabilized myocardial infarction. The position of the heart determines which standard lead shows T-wave inversion. The majority of hypertensive patients have the heart in the horizontal position, and therefore the inverted T wave is most commonly seen in Lead I. If the heart is vertical, even in the

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presence of left ventricular hypertrophy T-wave inversion will appear in Lead III, and in such cases the same feature is perhaps more commonly found in Lead II than in Lead I. It need scarcely be emphasized that T-wave inversion in Lead III alone is a frequent normal finding. The chest lead which shows T-wave inversion is necessarily in relation to the left ventricle, namely, the 4th, 5th, or 6th chest positions; the 5th position (anterior axillary line) is especially useful, and it

TABLE I

Analysis of Electrocardiograms of 218 Hypertensive Patients having Diastolic Blood-pressures of 100 mm. Hg or over

Electrocardiograms	*Total*	*Abnormality*	*Number of cases*
Normal	105		105
Abnormal with major changes	86	Inverted T wave in lead:	
		I alone	1
		II±III	2
		4 alone	2
		5 alone	15
		6 alone	3
		I+4±5±6	31
		I+II±III	2
		I+II±III+4±5	23
		II±III+4±5±6	3
		Anterior coronary occlusion	1
		Left bundle-branch lesion	3
Abnormal with minor changes	27	Low-voltage T waves only	6
		Depressed ST segments only	7
		Wide QRS	1
		High-voltage R wave in unipolar limb leads only	8
		Combinations of above changes	5

will be seen that 15 electrocardiograms showed inversion in this lead alone. No special significance should be attached to inversion of the T waves in several chest-lead positions as compared with inversion in a single chest lead. Analysis of such cases suggests no special degree of severity or exceptional clinical features, and the determining factor is again the position of the heart, and in particular the degree and direction of its rotation through its long axis. Left axis deviation by itself is commonly attributable to a heart in the horizontal position, and is generally related to obesity or to a stocky build with short chest and high diaphragm. Where high voltage of the R wave is seen in the left arm or left leg unipolar leads, an inference of left ventricular hypertrophy is justified. Outstandingly high voltage in the left ventricular chest leads may have the same significance, but varying thickness of the chest-wall is here a modifying element. The so-called 'transition point' in chest-lead electrocardiograms depends much on rotation of the heart, and should not necessarily be regarded as a guide to enlargement of one or other ventricle.

An example of an electrocardiogram showing the common form of major abnormality, or left ventricular 'strain pattern', is seen in Plate 1, Fig. 1. The T waves are inverted and ST segments depressed in standard lead I, in chest leads 4, 5, and 6, and in the left arm lead. There is marked left axis deviation and a high-voltage R wave (greater than 13 mm.) in the left arm unipolar lead.

Plate 1, Fig. 2, shows a minor abnormality of the electrocardiogram in a hypertensive patient. Here the low voltage of the T-waves in leads related to the left ventricle is the main feature. Such changes are generally antecedent to a later development of the full 'strain pattern'.

Analysis of Electrocardiographic Groups in Relation to Clinical Features

The first and obvious approach to an understanding of the meaning of electrocardiographic changes in hypertension is to discover whether these changes are

TABLE II

Electrocardiograms in relation to Sex, Age, and Habitus

Electrocardiograms	*Number of cases*	*Sex* (%)		*Habitus* (%)		*Age-group* (%)				
		Male	*Female*	*Obese*	*Normal*	*0–20 years*	*21–30 years*	*31–40 ,,*	*41–50 ,,*	*51–60 ,,*
Major abnormality	86	43	57	39	61	0	5	20	42	33
Minor abnormality	27	26	74	55	45	0	4	11	49	36
Normal	105	42	58	40	60	4	8	19	40	29

consistently associated with any special clinical feature. With this object an analysis was made of the main clinical features in our 218 patients, grouped according to their electrocardiographic status (Tables II to V). Percentage figures for the small group whose electrocardiograms showed minor abnormalities have obviously little meaning, and will not be discussed; they have, however, been included to complete the analysis. The two groups to be compared clinically are therefore the patients who showed major electrocardiographic abnormalities and those who showed none.

Sex. Despite the well-known fact that hypertension generally is a more severe disease in men than in women, the incidence of abnormal electrocardiograms was not biased by sex difference, the proportions of men and women in the two groups being almost identical.

Habitus. Any representative collection of hypertensive patients includes a considerable number of obese menopausal women, in whom the hypertension is usually benign. A high proportion of the obese patients in our series were of this type; but the incidence of electrocardiographic abnormalities was not affected by this fact.

Age. The age-incidence in the two groups is almost identical. In a study of this kind it is rarely possible to estimate the duration of hypertension in an individual patient, but it would seem reasonable to assume that as a general rule the older patients have been hypertensive the longest. Whether or not this is true, the older patients have not appeared especially liable to develop abnormal electrocardiograms.

Retinal Changes. The retinal changes, other than papilloedema, associated with hypertension are directly related to the condition of the retinal arteries,

which are presumed to be a fair sample of the arterial system as a whole, and might therefore be judged to afford indirect evidence of the state of the coronary arteries. Our grading of retinal change follows the practice introduced by Smithwick (1944): grade 0 = normal retinae; grade 1 = minor arterial changes (loss of light-reflex, variation of calibre, &c.); grade 2 = compression of the veins at arterial crossings; grade 3 = the presence of exudates or haemorrhages;

TABLE III

Electrocardiograms in relation to Retinal Change, Angina, and Albuminuria

Electro-cardiograms	*Number of cases*	*Retinal grade (%)*					*Angina (%)*	*Albuminuria (%)*
		0	*1*	*2*	*3*	*4*		
Major abnormality	86	1	27	41	12	19	33	44
Minor abnormality	27	15	29	37	15	4	22	30
Normal	105	5	40	39	6	10	20	36

grade 4 = papilloedema. The analysis shows a rather greater incidence of true retinopathy in the group of patients who have abnormal electrocardiograms.

Angina. Fifty-two patients (24 per cent.) in the whole series of 218 were judged to suffer from angina. The fact should not be overlooked that 21 anginal patients had normal electrocardiograms, though the incidence was certainly higher in the abnormal group.

Albuminuria. There is little difference between the two groups in respect of this finding.

Blood-pressure. 'Typing' of blood-pressure (Smithwick, 1944) is a somewhat arbitrary measure of pulse-pressure, Type 1 being a narrow pulse-pressure (less

TABLE IV

Electrocardiograms in relation to Blood-pressure

Electro-cardiograms	*Number of cases*	*Blood-pressure*				
		Type		*Diastolic level (mm. Hg)*		
		1 and 2 (%)	*3 (%)*	*100–20 (%)*	*121–40 (%)*	*Over 140 (%)*
Major abnormality	86	26	74	32	37	31
Minor abnormality	27	33	67	59	33	8
Normal	105	38	62	66	26	8

than half the diastolic pressure) and Type 3 a wide pulse-pressure (more than 20 mm. Hg greater than half the diastolic pressure). A wide pulse-pressure is presumed to indicate rigidity of the arterial system due to atheromatous and arteriosclerotic changes. A slightly higher proportion of patients with abnormal than with normal electrocardiograms showed a wide pulse-pressure, and a considerably higher proportion had severe diastolic hypertension. At the same time it is clear that severe hypertension is compatible with the maintenance of a normal electrocardiogram.

Heart size. It is conventional to speak of cardiac 'enlargement', since it is impossible to differentiate between the two components, dilatation and hypertrophy. The radiological assessment of cardiac enlargement is notoriously

difficult. Recognition of 'rounding' of the cardiac apex in the skiagram is insufficiently objective as an indication of left ventricular hypertrophy, and measurement of the transverse diameter of the heart shadow on a long distance film is unavoidable. If this measurement is related to the thoracic diameter without reference to the build of the patient, the interpretation is very likely to be wrong. In the present series the measured transverse diameter of the heart

TABLE V

Electrocardiograms in relation to Heart Size

(Computed from Hodges–Eyster formula)

		Heart	
Electrocardiograms	*Number of cases*	*Large* (%)	*Normal* (%)
Major abnormality	76	50	50
Minor abnormality	21	14	86
Normal	83	20	80

has been compared with the expected transverse diameter calculated from the Hodges–Eyster formula (1926), which is influenced by the height, weight, and age of the patient. A heart has not been recorded as enlarged unless its measured diameter has been at least 10 per cent. greater than the estimated diameter. On this basis the analysis (Table V) shows that a significantly greater proportion of patients with abnormal electrocardiograms had enlarged hearts, but even so this proportion was no higher than 50 per cent. On the other hand, it should be noted that 16 patients maintained normal electrocardiograms although their hearts were enlarged. Examples of this lack of correlation between cardiac enlargement and electrocardiographic change are seen in Plate 2, Figs. 3, 4, and Plate 3, Figs. 5, 6.

Summarizing the results of this survey, one can say little more than that an abnormal electrocardiogram appears more frequently in severe hypertension and in the presence of secondary arterial changes, cardiac enlargement, and angina, but that correlation with any of the clinical features studied is insufficient to justify any single deduction as to the cause of the electrocardiographic change. An equally negative conclusion was reached by Evans, Matthews, and White (1945) after their survey of a smaller group of hypertensive patients on rather similar lines. These authors found an association of abnormal electrocardiograms only with the degree of retinal change, the incidence of angina, and the long duration of hypertension.

The Cause of the Electrocardiographic Abnormality. Theoretical Considerations

Since the clinical study of a reasonably large and representative group of hypertensive patients does not explain the abnormalities which occur in their electrocardiograms, we are bound to consider what theoretical explanations are possible. There appear to be three possibilities deserving careful scrutiny, and these will be considered in order.

1. *That the abnormal electrocardiographic pattern is the expression of left ventricular muscle fatigue or strain due to work against high peripheral resistance.* The clinical analysis did not show a sufficiently close relationship between the blood-pressure level and the normality or abnormality of the electrocardiogram to suggest that this is a likely explanation. We have already seen that severely hypertensive patients can maintain normal electrocardiograms. As further evidence electrocardiograms were recorded from a small number of hypertensive patients under conditions in which their blood-pressure had been drastically lowered. Several of our early tests were made during deep sleep under sodium amytal narcosis. In one example the initial blood-pressure of 175/110 fell in the course of four hours to a minimum of 120/88. Electrocardiograms were taken at regular intervals, but the 'strain pattern' remained unaltered throughout this period. A more striking fall in blood-pressure may be achieved by the use of tetra-ethyl ammonium bromide. An example of this is shown in Plate 4, Fig. 7, where after intravenous injection of 0·3 gm. T.E.A.B. the blood-pressure fell within three minutes from 200/120 to 140/86. Again the 'strain pattern', recorded in the 5th chest position, did not alter. In view of these facts it seems certain that the abnormal electrocardiogram is not directly related to the raised blood-pressure, and therefore scarcely likely to result from muscle strain from this cause alone.

2. *That the electrocardiographic change is an expression of coronary insufficiency.* While one is bound to consider this hypothesis with care, it may in the first place be thought surprising that the incidence of angina was not higher among patients with abnormal electrocardiograms. But it cannot, of course, be held that the frequency of a subjective sensation such as anginal pain reflects the true incidence of coronary insufficiency. Here we need only remind ourselves that a bundle-branch lesion may commonly be found in a patient who has never experienced angina. In the second place, although it was shown by Evans and Hoyle (1933) that transient elevation of the T waves, or at least a lessened degree of T-wave inversion, may follow the use of vaso-dilator drugs, they were only able to achieve this effect in about half their patients, in spite of the fact that in the majority there was evidence of coronary insufficiency. Repeating this work more recently in a larger series of patients, Stokes (1946) had a similar degree of success, but was able to add the important information that the reversal of T-wave abnormality by vaso-dilators was as likely to occur in cases of uncomplicated hypertension as in myocardial infarction. Stokes was not prepared to offer any explanation for these findings, but we hope to show that they are capable of interpretation. It should not, however, be forgotten that there is evidence that the 'strain pattern' can, in fact, result from prolonged coronary insufficiency. An electrocardiogram recorded during a typical anginal attack seldom shows more than a transient depression of the ST segments, but East and Oram (1948) have recently drawn attention to episodes of prolonged cardiac pain which are almost certainly due to prolonged coronary spasm rather than to coronary thrombosis; in these cases the electrocardiogram shows a pattern quite distinct from that of coronary occlusion, and resembling closely the 'strain

pattern' seen in hypertensives. The subsequent complete reversal of these changes to normal emphasizes still further the different pathology of the two conditions. Nevertheless, the evidence in favour of coronary insufficiency as the basis of the 'strain pattern' in hypertension can only be regarded as equivocal.

3. *That the electrocardiographic changes associated with hypertension are due solely to the increased bulk of the left ventricular muscle.* In supporting this proposition Goldberger (1947) suggested that, owing to the increased bulk of the muscle, the exciting stimulus is delayed in its arrival at the surface of the ventricle, and the process of depolarization of the muscle is therefore also delayed. In these circumstances restoration of the muscle to the inactive state occurs in the order of its previous stimulation, and this abnormal state of affairs causes the T wave to point in a direction opposite to the preceding R wave, while the ST segment is depressed; these changes are accompanied by an increased voltage of the R wave and a prolongation of the QRS interval, due to the enlarged muscle. Goldberger somewhat weakened his case by admitting that in some electrocardiograms which show all the other features of the 'strain pattern' the widened QRS is not seen. In such cases he could do no more than suggest that some process of 'strain' must be responsible. In the 86 electrocardiograms of the present series which showed actual T-wave inversion, significant prolongation of the QRS interval was seen in only eight instances, which lends little support to the view that increased bulk of the left ventricle is, by itself, the basis of the abnormal electrocardiogram.

The Effects of Lumbo-dorsal Sympathectomy on the Hypertensive Electrocardiogram

There is virtually only one method by which the abnormal electrocardiogram in a hypertensive patient can be reversed, and this is by an effective sympathectomy. The striking improvement seen in the post-operative electrocardiograms in a high proportion of cases has been a feature of every report on the results of sympathectomy in hypertension. The first large series of cases were published independently by Smithwick (1944) and by Peet and Isberg (1946), who claimed that 63 per cent. and 52 per cent. respectively of previously abnormal electrocardiograms had been improved by operation. The author's own experience has been similar. Of 29 hypertensive patients submitted to operation and as yet adequately followed, 17 had abnormal electrocardiograms before operation, and 12 of these subsequently showed substantial improvement in this respect. An example is shown in Plate 4, Figs. 8 and 9. One might expect that the possibility of thus restoring a grossly abnormal electrocardiogram to normal would afford a clue as to why in the first place it had become abnormal. Experience of these patients before and after sympathectomy serves to emphasize certain points which seem of some importance. In the first place, improvement in the electrocardiogram appears almost invariably to be associated with a decrease in the size of the heart, where this was originally abnormal (Plate 5, Figs. 10, 11). Secondly, in many cases this improvement is delayed, or else is a gradual

TABLE VI

Summary of Progress of 11 Hypertensive Patients after Sympathectomy

	Pre-operative				Post-operative														
					First examination					Second examination					Later examination				
Case number	E.c.g. abnormality	Heart size (c/t ratio)	Blood-pressure		Interval	E.c.g. change	Heart size (c/t ratio)	Blood-pressure		Interval	E.c.g. change	Heart size (c/t ratio)	Blood-pressure		Interval	E.c.g. change	Heart size (c/t ratio)	Blood-pressure	
			lying	standing				lying	standing				lying	standing				lying	standing
1	Minor	1/1·9	236/127	252/136	4 weeks	Slight improvement	1/2·1	130/90	90/60	13 months	Further improvement	1/1·95	206/120	174/118	20 months	Normal	1/2·0	214/118	180/121
2	Minor	1/2·3	216/136	204/152	4 weeks	Normal	1/2·3	150/98	102/70	9 months	Normal	1/2·3	147/105	124/98	24 months	Normal	1/2·3	138/104	138/98
3	Major	1/1·95	190/130	170/130	3½ weeks	Slight improvement	..	130/95	75/65	2 months	Deteriorated	1/2·2	162/118	84/65	8 months	Great improvement	1/2·2	148/104	102/66
4	Major	1/1·75	260/151	260/165	3 weeks	No change	1/1·6	150/90	100/74	3 months	Deteriorated	1/1·6	210/117	146/94	22 months	Further deterioration (bundle-br. block)	1/1·6	210/120	160/100
5	Major	1/1·82	245/135	250/135	4 weeks	No change	1/2·03	180/120	70/50	6 months	Improved	1/2·6	193/115	200/120	24 months	Improvement maintained	1/2·0	233/130	236/130
6	Major	1/2·0	204/145	235/170	3 weeks	No change	..	190/120	100/70	2 months	No change	1/2·3	165/115	140/105	13 months	No change	1/2·0	183/124	146/90
7	Minor	1/2·25	242/108	198/128	2 months	Slight improvement	1/2·5	193/109	106/76	7 months	No change	1/2·5	180/110	155/108	..	..	..	..	..
8	Minor	1/2·0	200/129	212/150	3 months	Improved	..	148/95	80/50	7 months	Normal	1/2·15	140/95	98/70	24 months	Normal	1/2·15	190/123	158/116
9	Major	1/1·75	236/164	224/174	6 weeks	Improved	1/2·1	120/108	84/58	5 months	Further improvement	1/2·1	184/126	166/128	24 months	Further improvement	1/1·9	200/130	160/120
10	Major	1/2·1	190/118	178/136	2½ months	Slight improvement	1/2·1	230/138	150/120	8 months	Further improvement	1/2·1	220/134	170/128	..	..	..	..	..
11	Major	1/2·0	208/152	220/160	6 weeks	No change	1/2·0	145/119	125/105	10 months	No change	1/2·0	185/145	145/120	17 months	No change	1/2·0	210/145	160/140

process which only reaches its maximum several months after completion of the operation. This point is well illustrated by the example shown in Plate 6 (Figs. 12 to 14) in which the electrocardiogram was unchanged one month after operation, but five months later had considerably improved.

The preoperative state, and subsequent progress after operation, of a small series of hypertensive patients whose electrocardiograms were initially abnormal are summarized in Table VI. These cases have been selected for no reason other than that their first post-operative examination took place within a reasonably short interval from operation, and that their subsequent course covers an adequate period. For simplicity, the heart size has been recorded in terms of the cardio-thoracic ratio, which is perhaps adequate as a standard for comparative measurements. Average arm blood-pressures, both in the horizontal and in the upright position, at the time of each examination are included. Even this small number of cases reflects the unfortunate tendency of the blood-pressure to rise again gradually with the passage of time. But it will be seen that eight of the 11 patients retained a relative degree of postural hypotension at their last examination, as compared with their pre-operative blood-pressure when standing. The fact that most of these patients have so far maintained their functional improvement may be due to their diastolic pressure being lower, at least during the hours which they spend in an upright posture. On this assumption, and in the hope of prolonging the period of relief, it seemed reasonable to advise patients after sympathectomy to sleep as well propped-up as possible. Seven of these patients had definitely improved electrocardiograms after operation, and six of the seven showed the tendency, mentioned earlier, to a delayed or progressive improvement. With regard to heart size, all that one can fairly say is that of five cases in which the heart before operation was undoubtedly enlarged, it was subsequently smaller in all but one, and it is noticeable that in this case the electrocardiogram actually deteriorated, although the effect of sympathectomy on the blood-pressure was of the same order as in the other patients. The maintenance of electrocardiographic improvement, despite the eventual return of the blood-pressure to hypertensive levels, is yet further evidence that the abnormal electrocardiogram and the high blood-pressure are not directly related.

Summarizing the evidence of the effects of sympathectomy, it seems reasonable to infer that, since operation presumably does not alter the coronary circulation, the reversal of 'strain patterns' in the electrocardiogram is more likely to be related to a decrease in the size of the heart than to any other effect of operation.

Conclusions

It is well known that cardiac hypertrophy is due to enlargement of the individual muscle-fibres, not to the addition of fresh fibres. Harrison and Wood (1949) showed recently that when a heart hypertrophies there is a parallel increase in the size of its coronary arteries. This vascular development does not extend beyond the arteries, or at most the arterioles, for Roberts and Wearn

(1941) demonstrated by meticulous histological methods that the capillaries of the cardiac muscle increase only during the period of growth, and remain unchanged both in number and size despite enlargement of the muscle by hypertrophy. As a result of the increased size of the muscle-fibres, the concentration of capillaries in a given area of muscle is in fact much less in a hypertrophied heart than in a normal one. It is difficult altogether to refute the argument that decrease in the size of the heart after operation may in part be due to relief of dilatation, rather than to reduction of muscle. Judged by clinical standards the dynamic condition of the enlarged hearts in the present series has not pointed to dilatation as we understand it. Even if they were dilated, the change in size after operation is likely to be rapidly effected, and therefore cannot be causally related to the reversal of electrocardiographic abnormality which, as we have seen, tends to be a gradual process extending frequently over many months. On the other hand, it is possible to reconcile most of the apparently contradictory evidence which has been presented in this paper if the hypothesis is accepted that the improvement of the electrocardiogram after sympathectomy is associated with a decrease in the size of the heart by a gradual process of partial atrophy of previously hypertrophied muscle-fibres, and therefore with restoration of the normal relationship between muscle mass and capillary blood-flow. If this hypothesis is accepted, it will follow that the abnormal electrocardiographic pattern will appear whenever a sufficient number of cardiac muscle-fibres are inadequately irrigated. One can at present only speculate as to the physico-chemical mechanism which causes the electrocardiographic change, but Stoner, Green, and Threlfall (1948) presented evidence suggesting that electrocardiographic changes accompanying coronary occlusion may be due to the liberation of free phosphate groups by the breakdown of adenosine triphosphate during cardiac muscle ischaemia. If this process is concerned with the development of the 'strain pattern' electrocardiogram in hypertensive patients, all that can be said is that it has not so far been possible to alter that pattern by the intravenous injection of magnesium salts, although magnesium is known to inhibit dephosphorylation of adenosine triphosphate. It seems likely that the basis of the electrocardiographic change is an altered distribution of ions in the heart-muscle fibres, for it was shown by Bryant (1948) that potassium salts given in enormous dosage to hypertensive patients may effect a temporary improvement or reversal of the 'strain pattern' electrocardiogram, similar in character to the effects of sympathectomy.

However this may be, if the electrocardiographic change is due to cardiac muscle ischaemia it follows that two factors are involved: the size of the individual muscle-fibres, and the state of the coronary blood-supply. If this dual mechanism is conceded, it becomes easier to understand the relative lack of correlation between the development of an abnormal electrocardiogram and other important features such as the severity of the hypertension and the degree of cardiac enlargement. The unpredictable effects of vaso-dilator drugs on the electrocardiogram, which were mentioned earlier, also appear less puzzling in the light of this hypothesis. In any patient whose electrocardiogram shows the

'strain pattern', one or other of the two factors responsible for cardiac muscle ischaemia must be predominant, and in one type of case coronary dilatation may bring temporary relief of the ischaemia, while in the other it will clearly have no such effect. There is also no special difficulty in accounting for the appearance of identical 'strain pattern' electrocardiograms in patients suffering from certain forms of rheumatic heart disease unaccompanied by hypertension. A small survey of such cases has suggested that this pattern of electrocardiogram appears most frequently in association with aortic stenosis, with or without calcified valves, but in every case so far identified there has been unequivocal evidence of left ventricular hypertrophy. It should not be forgotten that, for mechanical reasons, in aortic stenosis defective coronary blood-flow may be an additional factor. If the size of the muscle-fibres and the coronary blood-flow are the two factors primarily concerned in cardiac muscle ischaemia, it seems probable from the evidence presented earlier that, in a hypertensive patient whose coronary circulation is unimpeded, the heart can hypertrophy to a relatively enormous extent before muscle ischaemia will cause the appearance of an abnormal electrocardiogram. On the other hand, if the 'strain pattern' appears when there is little or no cardiac enlargement, the inference must be that the coronary circulation is defective. In other words, the further a heart can hypertrophy before showing abnormal electrocardiographic patterns, the better is its coronary blood-supply. It will also follow that the finding of an abnormal electrocardiogram associated with obvious gross cardiac enlargement adds little to the physician's knowledge of the case, for a very large heart will outgrow its capillary blood-supply, with resulting muscle ischaemia, even if the coronary arteries remain healthy. In practice, when assessing the condition of hypertensive patients, it would seem advisable always to relate electrocardiographic changes to the degree of cardiac enlargement accompanying their first appearance, for this comparison is likely to give a true measure of the coronary circulation. From such data it may well be considered that the patient with the smaller heart has the worse prospects. It is the author's impression, from personal experience, that an occasional disaster might have been avoided if these principles had been observed in selecting certain hypertensive patients for sympathectomy.

Acknowledgements

It is a pleasure to acknowledge the helpful co-operation of my colleague Mr. James Hardman, who performed all the operations of sympathectomy in the present series. I am grateful also to Dr. R. S. Weetch and Dr. D. A. J. Tyrrell for their help in recording data at the hypertensive clinic. Finally I wish to thank Professor E. J. Wayne for his valued criticism and suggestions.

Summary

1. In a series of 218 hypertensive patients, 48 per cent. had normal electrocardiograms, 39 per cent. showed a major abnormality, and 13 per cent. showed minor changes.

2. Clinical analysis fails to show a close correlation between electrocardiographic abnormality and any single clinical feature.

3. There is little evidence that the electrocardiographic change is related singly to (*a*) left ventricular muscle 'fatigue', (*b*) coronary insufficiency, or (*c*) increased bulk of the heart-muscle.

4. From the author's experience of the reversal of abnormal electrocardiographic patterns after sympathectomy it is suggested that the electrocardiographic changes are an expression of cardiac muscle ischaemia, which is influenced both by the size of the individual muscle-fibres and by the efficiency of the coronary circulation.

5. The dual mechanism suggested would explain the indeterminate results of clinical analysis.

6. It is suggested that in assessing the condition of a hypertensive patient the presence of an abnormal electrocardiogram should be related to the size of the heart. If associated with a heart which is little enlarged, the inference is justified that the coronary circulation is impaired, but in the presence of gross cardiac enlargement this is not necessarily the case.

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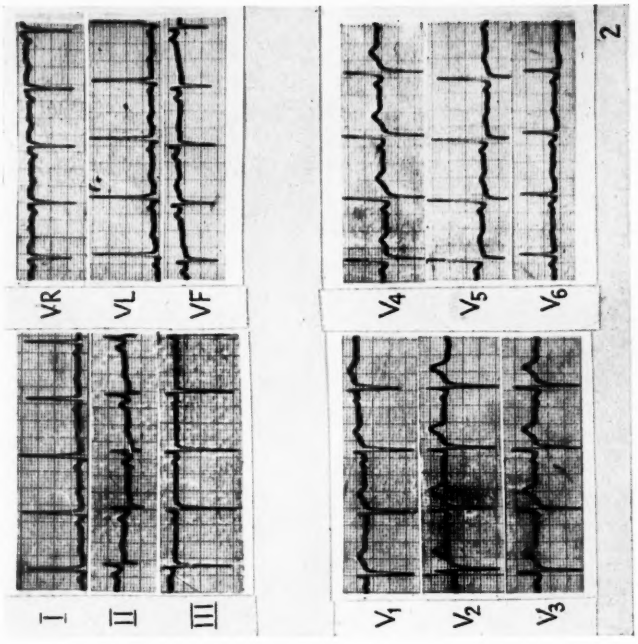


FIG. 2. Electrocardiogram showing minor abnormality

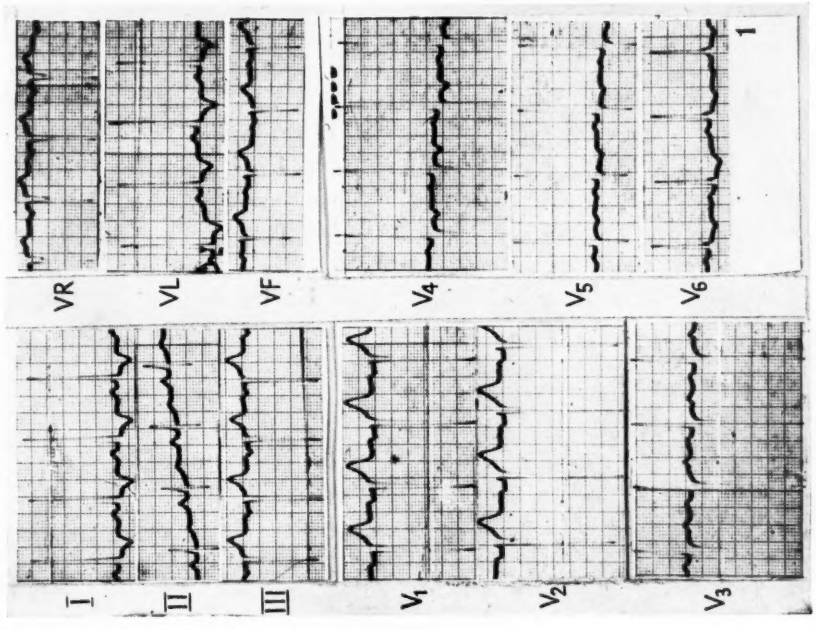


FIG. 1. Electrocardiogram showing major abnormality or strain pattern

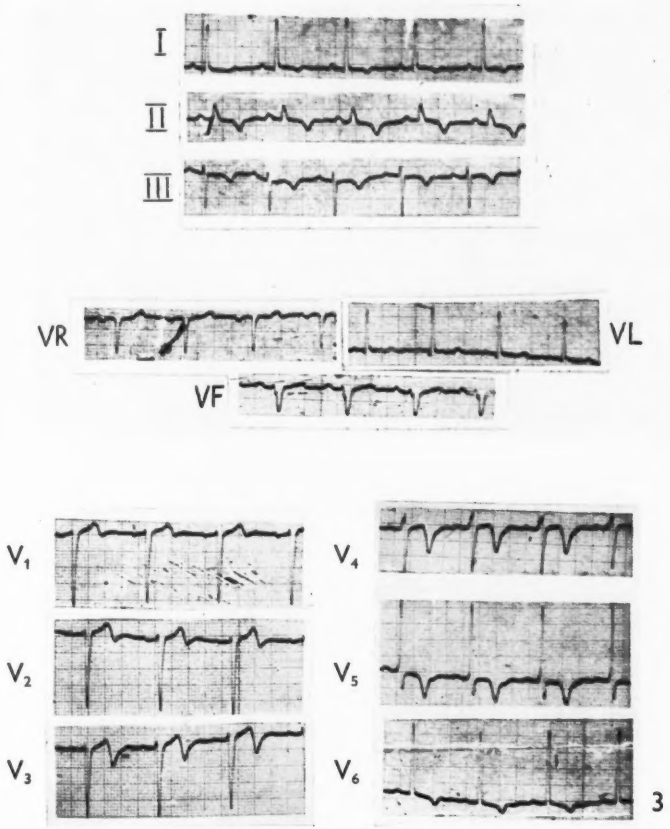


FIG. 3

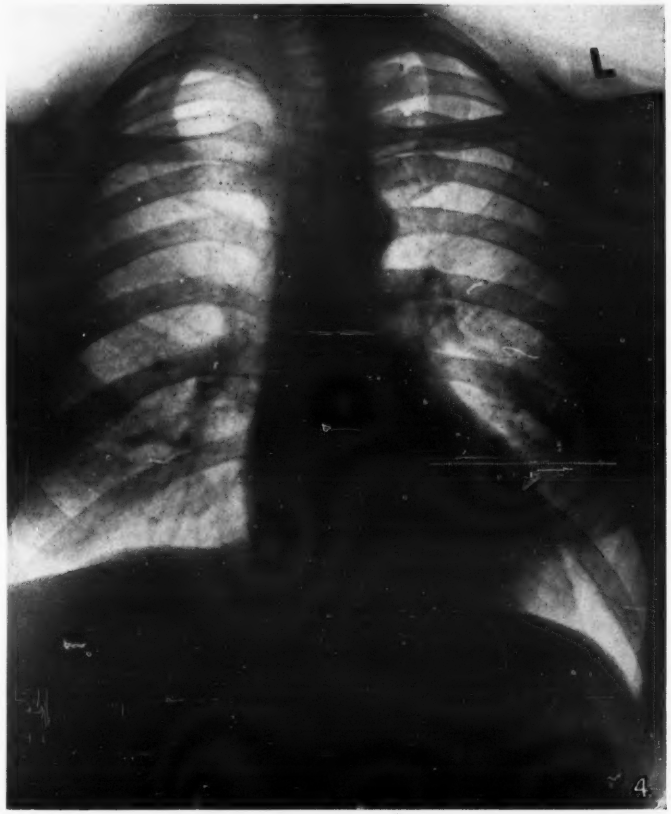
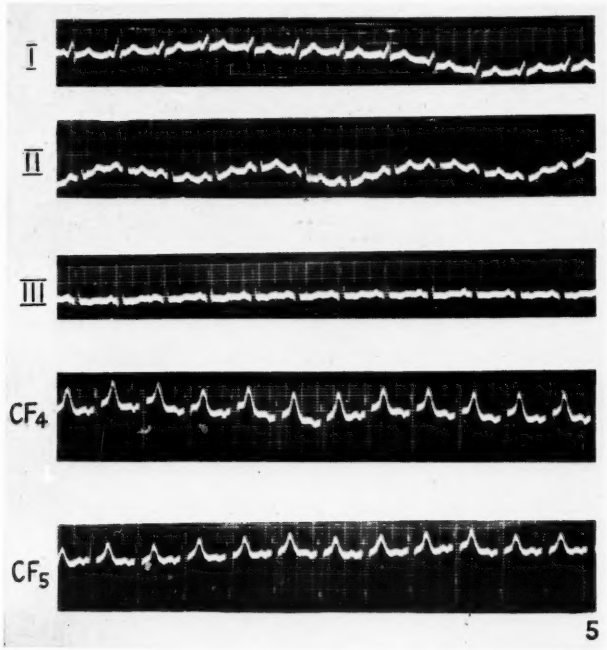
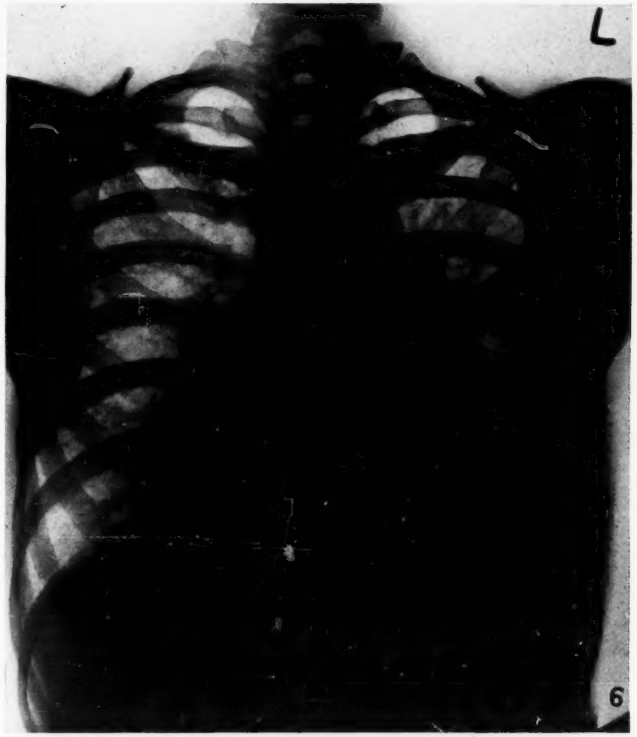


FIG. 4

'Strain-pattern' electrocardiogram with a normal-sized heart. Hypertensive patient; blood-pressure 190/110





FIGS. 5 and 6. Normal electrocardiogram with gross cardiac enlargement. Hypertensive patient; blood-pressure 262/166

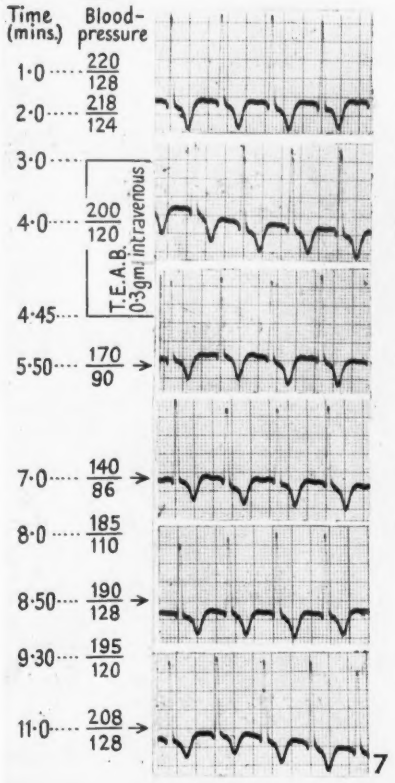
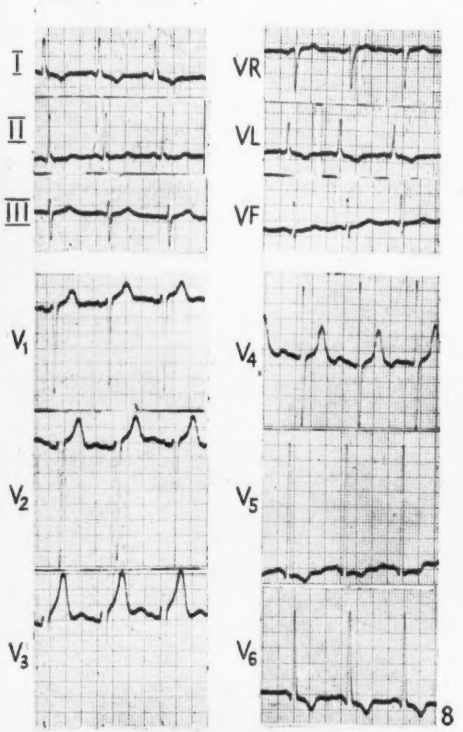
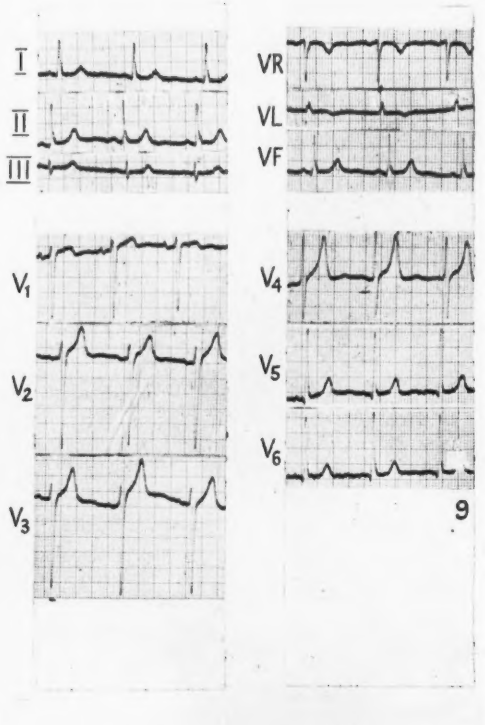
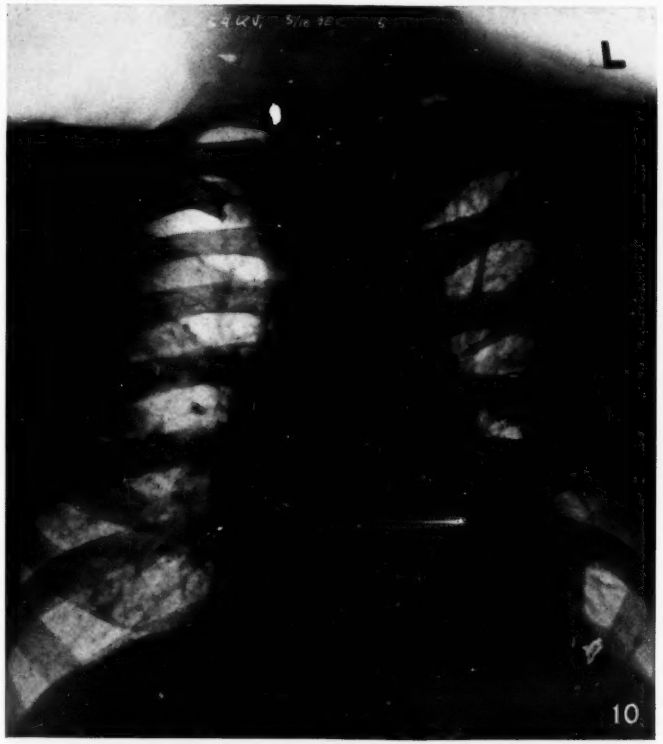


FIG. 7. Blood-pressure and e.c.g. (chest-lead 5) during and after tetra-ethyl ammonium bromide



Reversal of 'strain-pattern' electrocardiogram following sympathectomy. FIG. 8, before operation; FIG. 9, six months after operation





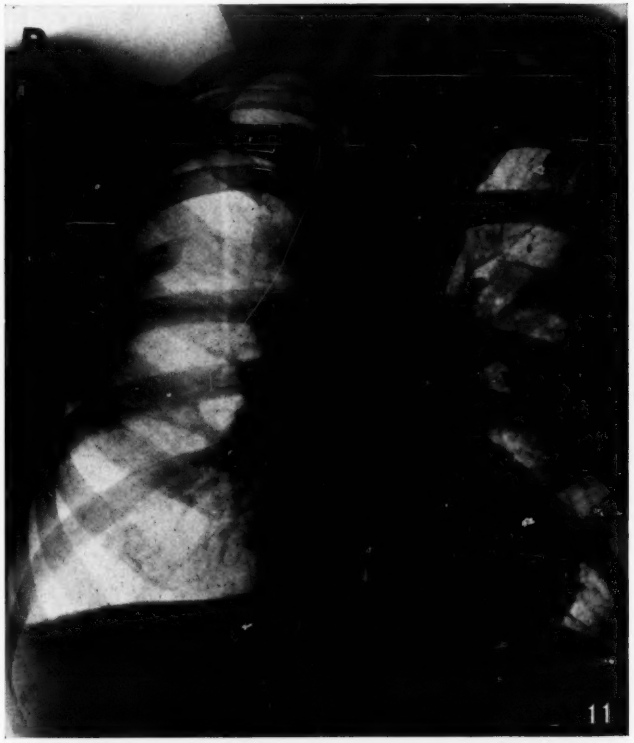


FIG. 10 FIG. 11

Reduction of heart size following sympathectomy; Fig. 10, before operation; Fig. 11, five months after operation

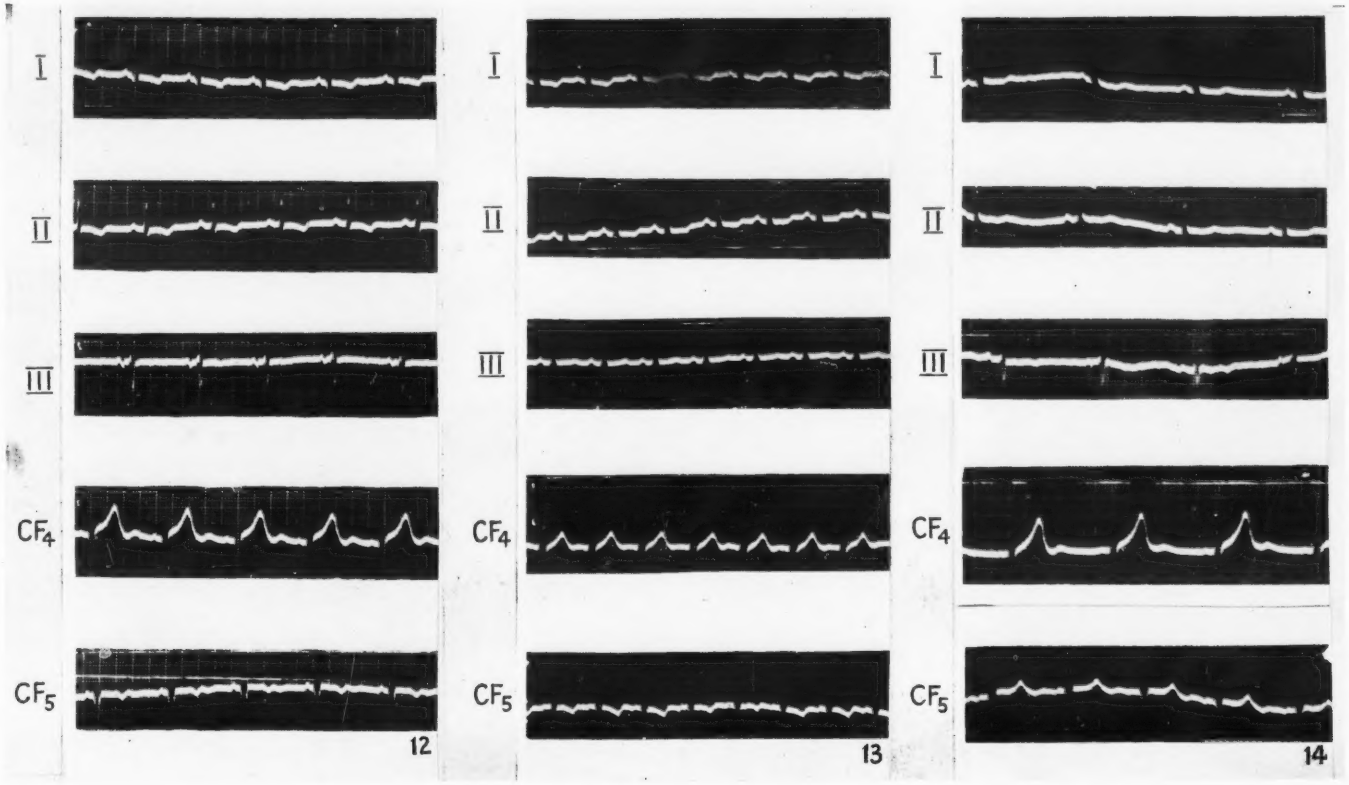


FIG. 12 FIG. 13 FIG. 14

Delayed improvement in electrocardiogram following sympathectomy. FIG. 12, 'strain pattern' before operation. FIG. 13, four weeks after operation (no change). FIG. 14, five months after operation

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CHOLINESTERASE ACTIVITY OF BLOOD AND MUSCLE IN MYASTHENIA GRAVIS[1]

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In myasthenia gravis one of the possible sources of disturbance at the neuromuscular junction is a loss of balance between the rate of liberation of acetylcholine and the rate of its destruction by cholinesterase. This aspect of the subject has been investigated by determining the cholinesterase activity of the blood and tissues of myasthenic patients, and by studying the effects of intra-arterial injections of acetylcholine (Harvey, Lilienthal, and Talbot, 1941; Wilson and Stoner, 1944, 1947; Acheson, Langohr, and Stanbury, 1948). Other workers (Torda and Wolff, 1944*a*, 1944*b*, 1945) have observed the effects produced on the synthesis of acetylcholine *in vitro* by the serum and cerebrospinal fluid of patients with myasthenia gravis. There is consistent and convincing evidence that at least two enzymes are responsible for destroying acetylcholine (Mendel, Mundell, and Rudney, 1943). True cholinesterase or acetylcholinesterase (Augustinsson and Nachmansohn, 1949), which is present in the red blood-cells, nervous tissue, and voluntary muscle of most animals and of man, is believed to be the enzyme responsible for the hydrolysis of acetylcholine liberated by nervous activity (Hawkins and Gunter, 1946). Pseudo-cholinesterase, which is present in the plasma of human subjects, is capable of hydrolysing other esters in addition to acetylcholine. Previous systematic studies of the blood-cholinesterase activity of myasthenic patients have been concerned with the enzyme activity of the serum only, that is, with the activity of pseudo-cholinesterase. In the majority of instances the pseudo-cholinesterase of the serum has been shown to be within normal limits, although in a few cases values higher or lower than normal have been reported. The work referred to has been discussed in this journal (Wilson and Stoner, 1944) and has been recently reviewed by Augustinsson (1948). The object of the present investigation was to determine the activities of pseudo-cholinesterase and of true cholinesterase in the blood and skeletal muscle of patients with myasthenia gravis and of normal subjects. The mode of action of true cholinesterase in the blood and skeletal muscle of myasthenic patients has been studied in order to determine whether it differs from that found in normal subjects.

Methods

Specimens of venous blood were taken from 100 normal healthy adults, and from 19 patients with the typical signs and symptoms of myasthenia gravis

[1] Received June 26, 1950.

who had not received neostigmine for at least 12 hours prior to the removal of the blood sample. Immediately after venepuncture specimens of blood were transferred to bottles containing heparin as an anticoagulant, and were centrifuged. The plasma was separated, and the red cells, after being washed twice with normal saline, were laked with distilled water. The cholinesterase activity of each specimen of plasma and of red cells was determined manometrically, in duplicate, at 38° C. by the method of Mendel, Mundell, and Rudney (1943), using the specific substrates, benzoylcholine chloride 0·006 M for the estimation of pseudo-cholinesterase, and acetyl-β-methylcholine chloride 0·03 M for true cholinesterase. Cholinesterase activity is expressed as the amount of carbon dioxide in μl. liberated in 60 minutes from one ml. of plasma or one ml. of laked red-cell preparation. Two major difficulties were encountered in determining the cholinesterase activity of skeletal muscle. The amount of muscle necessary for adequate determinations could not be obtained by ordinary methods of biopsy under local anaesthesia. In the case of patients with myasthenia gravis, advantage was taken of an opportunity provided by Mr. Geoffrey Keynes to procure specimens of pectoralis major, which were obtained in the course of operations for thymectomy. Although in many instances weakness of this muscle could be demonstrated, we were unable to devise a satisfactory quantitative method of assessing the extent to which the muscle specimen was affected by the disease. It was not possible to obtain specimens of a similar muscle-group from normal subjects for purposes of comparison, but specimens of latissimus dorsi were provided by Professor Pilcher. These specimens were excised during operations under cyclopropane or nitrous oxide anaesthesia. Each sample of muscle was kept on ice until the estimation was carried out, usually within one hour. The muscle was dissected free from fat and other extraneous tissue, washed twice with buffer solution, and cut into small particles. A fine suspension of the sample in buffer solution was then made with a high-speed homogenizer, and the suspension, containing 100 mg. of muscle per ml., was gassed with nitrogen-carbon dioxide mixture for two minutes. The composition of the buffer solution used was NaCl 0·15 M, $MgCl_2$ 0·04 M, and $NaHCO_3$ 0·025 M in distilled water. Determinations of pseudo- and true cholinesterase activity were made in duplicate, using 2 ml. of muscle-suspension in 3·6 ml. of buffer solution in the main vessel. The substrates, benzoylcholine chloride (0·006 M) or acetyl-β-methylcholine chloride (0·03 M), were placed in the side arm, so that the total volume of liquid in each vessel was 6 ml. After gassing the manometer vessels with nitrogen-carbon dioxide mixture for three minutes and equilibrating, they were tipped and readings were taken at 15, 30, 45, and 60 minutes. The results were calculated from the readings taken during the period 30–60 minutes, and the cholinesterase activity was expressed as the amount of CO_2 in μl. liberated from 1 gm. (wet weight) of muscle in 60 minutes.

Results

Blood-cholinesterase activity. Since the true cholinesterase of plasma and the pseudo-cholinesterase of red cells represent a small proportion (1 to 5 per cent.)

of the cholinesterase activity in blood (Mendel, Mundell, and Rudney, 1943; Maw and Wilson, unpublished), the results reported here are concerned only with the pseudo-cholinesterase activity of plasma and the true cholinesterase activity of red cells. Table I shows the activities of pseudo-cholinesterase in the plasma, and of true cholinesterase in the red cells, of normal subjects and of

TABLE I

Pseudo-cholinesterase Activity in the Plasma and True Cholinesterase Activity in the Red Cells of Normal Subjects and of Patients with Myasthenia Gravis

Source of enzyme	*Number of subjects*	*Range of activity* (μl. CO_2/ml./hr.)	*Mean*	*t*	*P*
Pseudo-cholinesterase					
Normal plasma	100	818–3,265	1,722	0·8	0·4
Myasthenic plasma	19	920–2,677	1,625		
True cholinesterase					
Normal red cells	100	1,226–2,376	1,762	0·06	1·0
Myasthenic red cells	19	1,196–2,177	1,758		

patients with myasthenia gravis. There is a wide range of pseudo-cholinesterase activity in normal subjects (818 to 3,265, mean value 1,722), and of myasthenic patients (920 to 2,677, mean value 1,625). These results, when analysed statistically, show that there is no significant difference in the plasma pseudo-cholinesterase activity of the two groups. There is also a wide range of true cholinesterase activity in normal subjects (1,226 to 2,376, mean value 1,762) and in myasthenic patients (1,196 to 2,177, mean value 1,758). These mean values do not differ significantly. This is in agreement with the recent findings of Grob, Lilienthal, Harvey, and Jones (1947).

Experiments were carried out with the red cells of normal subjects and of myasthenic patients in order to determine whether the mode of action of true cholinesterase from the two sources is identical. The following relationships were studied: (1) enzyme activity and the concentration of substrate, and (2) enzyme inhibition *in vitro* and the concentration of inhibitor. Neostigmine methylsulphate (neostigmine) and di-isopropylfluorophosphonate (DFP) were used as inhibitors.

1. The enzymatic hydrolysis of acetyl-β-methylcholine chloride by true cholinesterase was investigated in various concentrations of the substrate, and curves were plotted of the rate of hydrolysis (v) against the negative logarithm of the molar concentration of substrate (pS). Fig. 1 shows typical curves for this enzyme in the red cells of a normal subject and in those of a patient with myasthenia gravis. For true cholinesterase in normal red cells the optimum pS is 1·4, and the Michaelis constant, K_m, which is the value of pS at which half-velocity is attained, is 2·5. As will be seen from Fig. 1, the enzymes from the two sources have the same pS and K_m values.

2. The inhibition *in vitro* of true cholinesterase activity in normal and myasthenic red cells by neostigmine and by DFP was determined. In each case the

inhibitor was added to the enzyme-buffer solution 30 minutes before the addition of substrate. The percentage inhibition of activity was plotted for various concentrations of inhibitor. Table II gives data obtained from the curves for each inhibitor, and shows the negative logarithm of the molar concentration of inhibitor (*pI*) required to produce 25 per cent. and 65 per cent. inhibition. There is close agreement between the results obtained with normal and with myas-

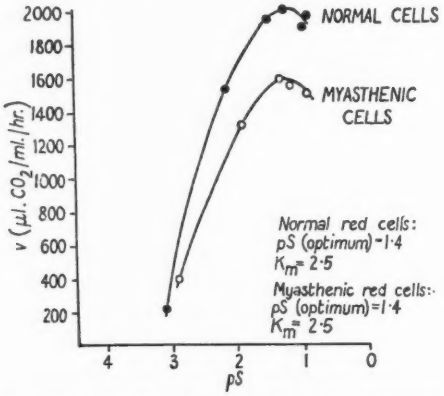

FIG. 1. Activity/*pS* curve for the enzymatic hydrolysis of acetyl-β-methylcholine chloride by true cholinesterase in normal and in myasthenic red cells.

thenic red cells. When these results are considered in conjunction with the evidence obtained from the activity/*pS* curves, there appears to be no funda-

TABLE II

The Inhibition (in vitro) *of True Cholinesterase Activity in Normal and Myasthenic Red Cells by Neostigmine and by DFP*

Source of enzyme	*Neostigmine*		*DFP*	
	pI_{25}	pI_{65}	pI_{25}	pI_{65}
Normal red cells . . .	8·5	7·2	7·2	6·7
Myasthenic red cells . .	8·7	7·2	7·1	6·7

pI is the negative logarithm of the molar concentration of inhibitor required to produce 25 per cent. or 65 per cent. inhibition.

mental difference, as regards the mode of action of true cholinesterase, between normal and myasthenic red cells.

Cholinesterase activity of skeletal muscle. In most instances the patients with myasthenia gravis had been given neostigmine within two hours of removal of the muscle specimen. The possibility had therefore to be borne in mind that the cholinesterase activity of the muscle might be inhibited by neostigmine. This inhibition was considered to be unlikely, since it did not occur in specimens of blood withdrawn at the same time as the muscle was removed. Goodman, Carlson, and Gilman (1939) showed that eserine has a greater affinity *in vitro*

for serum than for muscle-cholinesterase, and that *in vivo* there is no preferential inhibition of muscle-cholinesterase. The activity of pseudo-cholinesterase in human skeletal muscle is very low, and in some specimens there was no evidence of any activity. In myasthenic muscle the range of activity was 0–112, with

TABLE III

Cholinesterase Activity in Skeletal Muscle of Normal Subjects and of Patients with Myasthenia Gravis

Source of enzyme	*Number of subjects*	*Range of activity* ($\mu l.CO_2/ml./hr.$)	*Mean*	*t*	*P*
Pseudo-cholinesterase					
Normal muscle	8	0—129	60	0·4	0·7
Myasthenic muscle	10	0—112	49		
True cholinesterase					
Normal muscle	14	519—1,378	988	1·84	<0·1
Myasthenic muscle	14	260—1,287	796		>0·05

a mean value of 49, which was not significantly different from that of normal muscle (Table III). The true cholinesterase activity of muscle is of a much

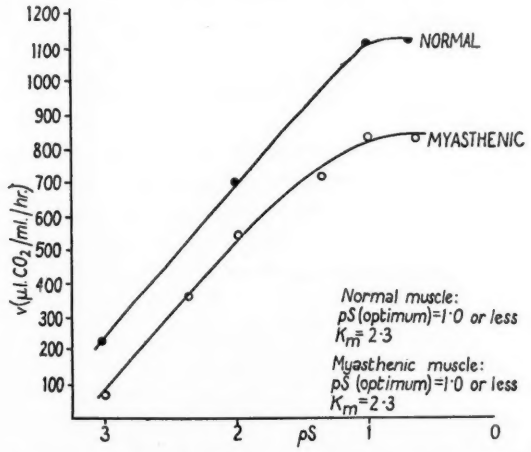

FIG. 2. Activity/*pS* curve for the enzymatic hydrolysis of acetyl-β-methylcholine chloride by true cholinesterase in normal and myasthenic skeletal muscle.

higher order, ranging in the case of myasthenic muscle from 260 to 1,287, compared with 519 to 1,378 for normal muscle; the respective mean values were 796 and 988. Statistical analysis of these results indicates that myasthenic muscle has an activity not significantly lower than normal muscle.

The mode of action of true cholinesterase in normal and myasthenic skeletal muscle was studied by examining the relationships between activity and substrate-concentration, and the relationships between inhibition and the concentration of neostigmine and of DFP.

1. The activity/substrate-concentration curves were plotted for true cholinesterase, and typical curves obtained from samples of normal and of myasthenic muscle are shown in Fig. 2. In each case optimum activity occurred at 10^{-1} M acetyl-β-methylcholine chloride ($pS = 1$). At higher concentrations of substrate both curves flattened out. It was not possible, under the experimental conditions used, to obtain values for concentrations of acetyl-β-methylcholine chloride

TABLE IV

The Inhibition (in vitro) *of True Cholinesterase Activity in Skeletal Muscle of Normal Subjects and of Patients with Myasthenia Gravis*

Source of enzyme	*Neostigmine*		*DFP*	
	pI_{25}	pI_{65}	pI_{25}	pI_{65}
Normal muscle . . .	7·3	6·8	7·3	6·5
Myasthenic muscle . . .	7·1	6·6	7·4	6·4

pI is the negative logarithm of the molar concentration of inhibitor required to produce 25 per cent. or 65 per cent. inhibition.

greater than 3×10^{-1} M. The value for the Michaelis constant (K_m) is 2·3 for each group. The K_m and optimum pS of muscle-cholinesterase differ from those obtained with red-cell cholinesterase, but it is possible that the difference is due to the presence of Na and Mg ions in the buffer solution used for estimating muscle-cholinesterase, since Mendel and Rudney (1945) have shown that the addition of certain salts to the buffer solution causes a decrease in the optimum pS.

2. The effects of neostigmine and DFP on the inhibition *in vitro* of true cholinesterase in muscle were examined in a manner similar to that already described for red cells. Table IV shows that for both inhibitors the pI values in myasthenic muscle corresponding to enzyme inhibitions of 25 per cent. and 65 per cent. are in close agreement with those in normal muscle.

Discussion

The evidence so far obtained indicates that the cholinesterase activity of myasthenic skeletal muscle is not significantly different from that of normal muscle. Furthermore, the enzymes from each source appear to be identical with regard to the characteristics examined. The results of this work do not warrant any conclusion as to whether the release of acetylcholine at the nerve-endings is diminished, for instance, by functional denervation, since Couteaux and Nachmansohn (1938) have shown that in the guinea-pig the denervation of skeletal muscle does not significantly reduce its cholinesterase activity. Our results, however, strengthen the conclusion that the fault in myasthenia gravis does not lie in an abnormally rapid destruction of acetylcholine. More precise information concerning the cholinesterase activity of the motor end-plates is necessary before this conclusion can be completely sustained.

It is a pleasure to acknowledge the help we have received from Mr. Geoffrey Keynes and Mr. J. E. Piercy (New End Hospital), and from Professor Pilcher

(University College Hospital) who provided specimens of skeletal muscle. We are indebted to Miss Nancy Leach and Miss Barbara Allen for technical assistance. Dr. B. C. Saunders (University of Cambridge) kindly supplied specimens of DFP, and Dr. F. Bergel (Roche Products, Ltd.) specimens of benzoylcholine chloride. The expenses of this work were partially defrayed by a grant from the Medical Research Council, and also by the Ministry of Supply, from whom one of us (H. G.) is in receipt of a whole-time grant.

Summary

1. The activity of pseudo-cholinesterase in plasma and that of true cholinesterase in red cells, determined in 19 patients with myasthenia gravis, were found not to differ significantly in range or in mean value from those observed in 100 normal subjects.

2. The activity of pseudo- and of true cholinesterase in skeletal muscle was determined in specimens of pectoralis major taken from myasthenic patients, and in specimens of latissimus dorsi from normal subjects. Pseudo-cholinesterase activity was found to be very low both in normal and in myasthenic subjects. True cholinesterase activity varied over a wide range, but there was no statistically significant difference between the mean values for the two groups.

3. The modes of action of true cholinesterase in the blood and skeletal muscle of myasthenic patients do not appear to differ from those found in normal subjects.

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CHOLINESTERASE INHIBITION AND SIGNS AND SYMPTOMS IN MYASTHENIA GRAVIS[1]

By ANDREW WILSON, G. A. MAW, and HONOR GEOGHEGAN

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One of the fascinating features of myasthenia gravis is the dramatic, though transient, relief of symptoms produced in patients with this disease by an injection of neostigmine. The action of neostigmine is usually attributed to its inhibition of cholinesterase activity; if this is a true explanation, then di-isopropylfluorophosphonate (DFP), which is a potent and irreversible inhibitor, might be expected to produce even more dramatic and prolonged clinical effects. The work to be described has been concerned with comparing the inhibitory effects on blood-cholinesterase produced by DFP and by neostigmine in patients with myasthenia gravis, and with establishing what relationship, if any, exists between these effects and the clinical response to the two drugs. Three types of observation have been made:

1. The immediate clinical effects and simultaneous changes in blood-cholinesterase activity produced by an intramuscular injection of neostigmine were compared with those which resulted from an intramuscular injection of DFP.
2. The immediate effects on the action potential of the small muscles of the hand, and the ensuing changes in blood-cholinesterase activity, produced by an injection of neostigmine into the brachial artery were compared with those obtained with a similar injection of DFP.
3. DFP in small doses was administered for prolonged periods, and the clinical effects and concomitant changes in blood-cholinesterase activity were studied.

Methods

Ten patients with myasthenia gravis were studied. The true cholinesterase activity of red cells and pseudo-cholinesterase activity of plasma were determined by the technique already described (Wilson, Maw, and Geoghegan, 1951). The extensive theoretical considerations of Straus and Goldstein (1943) have re-emphasized the distinction between reversible and irreversible inhibitors of enzyme activity. These workers found, when estimating the inhibition of serum-cholinesterase in the dog, using acetylcholine as substrate and physostigmine as inhibitor, that dilution of the samples produced considerable decreases in

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inhibition owing to dissociation of the enzyme-inhibitor complex. In the present experiments it was therefore anticipated that the enzyme inhibition observed might be lower than that actually occurring *in vivo*. It was found, however, that the procedure involved in our technique of washing red cells with saline did not alter the cholinesterase activity either in the presence or in the absence of inhibitor. Furthermore, studies which we have made of the inhibition of human blood-cholinesterase activity by neostigmine indicate that, under our experimental conditions, the dissociation brought about by dilution of the inhibitor-enzyme complex is negligible. No correction factor has therefore been applied to the results obtained for inhibition with neostigmine. In the short-term observations our patients were kept in bed, and neostigmine therapy was withdrawn for as long a period as possible. To minimize the muscarinic effects of the drugs, 0·5 mg. of atropine sulphate was given subcutaneously 15 minutes before the observations were started. The DFP used was a freshly prepared saline solution containing 1 mg. per ml.; the neostigmine used was the methylsulphate, and the doses given refer to the salt. When the dose was given by mouth neostigmine bromide was used. In the long-term observations the patients were allowed to get up when able; during the initial treatment neostigmine was withheld. The DFP was dissolved in arachis oil and given daily intramuscularly, preceded in some cases by subcutaneous injections of 0·5 to 1·0 mg. atropine sulphate.

Results

1. *Effects of neostigmine and of DFP given intramuscularly.* The effects produced by neostigmine (1·5 mg. in 0·8 ml.) were observed in each patient, and two days later each experiment was repeated under similar conditions with DFP (0·5 mg. in 0·5 ml.) in place of neostigmine. Venous blood was withdrawn from the left arm before, and 30, 60, and 90 minutes after the intramuscular injection of the drug into the right arm. Fifteen minutes after injection of neostigmine there was marked relief of ptosis and dysphagia, and a generalized increase in muscle strength; the effect lasted for about 80 minutes. In contrast, there were no changes in signs and symptoms during a similar period of observation after injection of DFP. The changes produced in the cholinesterase activity of blood in a typical case are shown in Fig. 1. It is seen that with neostigmine, during the period of clinical response, the pseudo-cholinesterase activity of plasma was inhibited to a maximum of 35 per cent., and when the myasthenic signs and symptoms had reappeared inhibition was still about 20 per cent. This agrees with previous observations (Wilson and Stoner, 1944). In contrast, the inhibition of pseudo-cholinesterase by DFP was almost double that produced by neostigmine, and continued to increase. The inhibitory effect of each drug on true cholinesterase activity was very slight, and in the case of neostigmine the effect was at its maximum when the myasthenic signs and symptoms had reappeared. From these results it appears that the relief of signs and symptoms is not directly related to the inhibition of pseudo-cholinesterase activity in plasma, and that the inhibition of true cholinesterase activity in red cells is not a significant factor in the clinical response.

2. *Effects of neostigmine and of DFP given intra-arterially.* These observations were carried out in conjunction with Dr. P. Merton, of the National Hospital for Nervous Diseases, Queen Square, London. The action potentials of the small muscles were recorded in both hands. The ulnar nerve was stimulated continuously at the wrist with condenser shocks, maximal for the motor fibres, at the rate of two per second. The action potentials were led off from the hypothenar

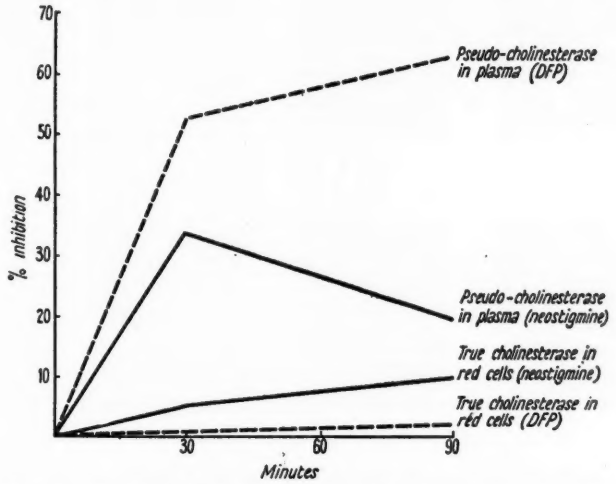

FIG. 1. The inhibition of true and pseudo-cholinesterase activity in the red cells and plasma of a myasthenic patient by neostigmine (1·5 mg.) and by DFP (0·5 mg.) given intramuscularly.

eminence of each hand, amplified as cathode-ray traces, and photographed. Fatigue of the muscles usually occurred after 10 minutes' stimulation, and when it occurred either 1 mg. neostigmine or 1 mg. DFP, in 2 ml. saline, was injected into the right brachial artery. Specimens of venous blood were withdrawn from the left and right arms before and 15 minutes after each injection. Fig. 2 shows typical cathode ray traces obtained before and after administration of the two compounds. After neostigmine the muscle action potential from the injected arm was restored to the resting state within 30 seconds, and about 10 minutes later a similar effect was observed in the non-injected arm; these effects lasted for about 80 minutes. When DFP was used, a response in the injected arm similar to that which occurred with neostigmine was seen within 30 seconds, and this effect was still present four days after the injection; in the non-injected arm no effect was noticed even after a period of one hour. Determinations of true and pseudo-cholinesterase activity in blood taken from the left and right arms showed that the changes in enzyme activity were similar in each arm. Fig. 3 represents the mean changes in cholinesterase activity obtained from five experiments. It is seen that the average inhibition of the pseudo-cholinesterase of plasma produced by neostigmine was approximately 36 per cent. (range 35 to 37 per cent.); while that produced by DFP was approximately 91 per cent.

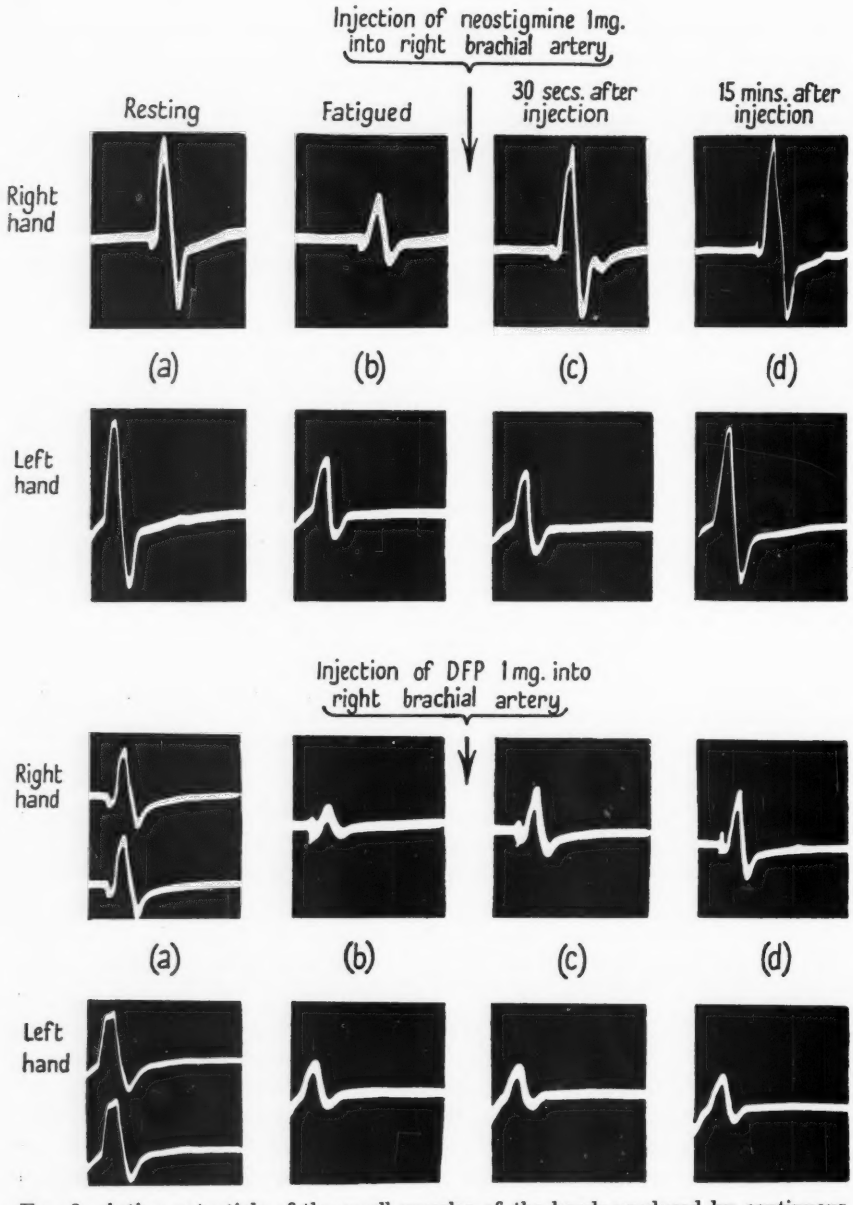

FIG. 2. Action potentials of the small muscles of the hands produced by continuous stimulation of the ulnar nerve at the wrist, with condenser shocks maximal for the motor fibres at the rate of two per second. (*a*) On first stimulating; (*b*) after 10 minutes' stimulation; (*c*) 30 seconds after injection of drug into right brachial artery; (*d*) 15 minutes after injection.

(range 70 to 100 per cent.). In the case of the true cholinesterase of red cells, DFP produced an average inhibition of 21 per cent. (range 14 to 26 per cent.) in each arm, compared with three per cent. (range one to five per cent.) by neostigmine; it is noteworthy that the 21 per cent. inhibition did not result in any change in the action potentials of the muscles in the non-injected arm, whereas with neostigmine the effect was seen with only three per cent. inhibition. These

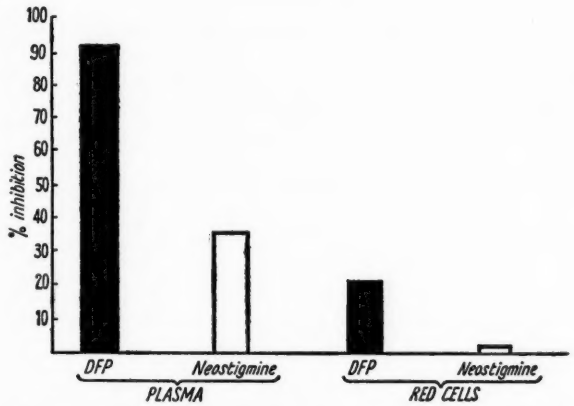

FIG. 3. The mean inhibition of cholinesterase activity in the plasma and red cells of myasthenic patients 15 minutes after the intra-arterial injection of 1 mg. of (*a*) DFP and (*b*) neostigmine.

results recall those obtained by Brown, Burns, and Feldberg (1948) in the twitch response of the cat's tibialis anticus muscle. An intravenous injection of DFP was practically ineffective, whereas an arterial injection caused an augmented twitch tension due to repetitive firing of the muscle fibres. In contrast, eserine and neostigmine were effective by the intravenous route.

3. *Effects of prolonged intramuscular administration of DFP.* We have seen that in myasthenic patients the clinical response to a single injection of DFP varies according to the route of administration. Given intramuscularly, a single injection produced no clinical response; by arterial injection a long-lasting effect was obtained, but was confined to the muscles supplied from the injected artery. It was hoped to obtain long-lasting and general effects by giving small daily doses of DFP intramuscularly for long periods. The observations were begun during the war, and have previously been reported in part (Gaddum and Wilson, 1947). A similar approach to the problem has been made in the U.S.A., and other workers have recorded clinical studies of the same kind (Comroe, Todd, Gammon, Leopold, Koelle, Bodansky, and Gilman, 1946; Comroe, Todd, and Koelle, 1946; Harvey, Lilienthal, Grob, Jones, and Talbot, 1947).

The histories of the 10 myasthenic patients observed are summarized in the Table. The daily dose of DFP was 0·5 to 1 mg. The treatment produced no sudden changes in signs and symptoms, but after 10 to 15 days most patients

showed a gradual and sustained increase in the muscle strength of the limbs, and the dynamometer readings of the hand increased by 50 to 100 per cent. This effect was well illustrated by the absence of muscle weakness in the morning, which enabled patients to rise, dress, and walk about, when previously they had not been able to do so until they had taken neostigmine. The increase in muscle strength was not as intense as the maximum effect produced by neostig-

TABLE

Summary of the Case Histories of 10 Patients Treated with DFP Daily

Case number	*Sex*	*History of myasthenia*	*Muscular weakness*		*Remission*	*Neostigmine daily dose (mg.)*	*Duration of DFP treatment (months)*	*Remarks*
			Cranio-pharyngeal	*Peripheral*				
1	M	3 yrs.	+	++	0	20 subcut.	36	Relief sustained without neostigmine
2	F	11 yrs.	+	++	2 periods of 6 mths.	3 subcut.	34	Partial relief without neostigmine
3	F	11 yrs.	++	++	1 of 3 weeks	120 oral	2 weeks	Toxic effects. No relief of dysphagia
4	F	6 mths.	++	+	0	120 oral	4 weeks	No relief of dysphagia
5	M	2 yrs.	++	++	0	150 oral	24	Weakness of wrists persistent
6	F	3 yrs.	+	++	for 1 yr. after thymectomy	90 oral	5 weeks	Toxic effects
7	F	6 mths.	++	+	0	120 oral	8 weeks	Toxic effects. No relief of dysphagia
8	F	1 yr.	+	++	0	75 oral	24	Satisfactory with 30 mg. neostigmine daily
9	F	6 mths.	+	++	0	75 oral	16	Dysphagia. Relief by X-rays to thymus later
10	F	15 yrs.	+	++	for 3 mths. after thymectomy	150 oral	3	Partial relief. 75 mg. neostigmine daily

mine. Relief of ptosis, diplopia, and dysphagia was much slower in onset, and usually did not occur until after at least six weeks' treatment. The effect was so slight in some patients that further treatment with DFP was abandoned. After six weeks the dose of DFP was usually given every second or third day, and in two patients the drug was eventually given every fourth day. The period of observation during treatment varied from two weeks to two and a half years. Two patients have continued treatment for two and a half years, two for two years, and one for three months. One patient (Case 9), despite treatment with DFP for 16 months, became very weak and had marked bilateral ptosis, dysphagia, and dyspnoea on slight effort. She responded well, however, to injections of neostigmine. This patient had a well-defined mediastinal shadow which was regarded as due to a tumour of the thymus. DFP was discontinued, and after a period of X-ray therapy her condition showed considerable improvement and she had marked relief from dysphagia and dyspnoea. The treatment of four other patients was stopped because of failure to relieve symptoms or on account of toxic effects, the most troublesome of which were tightness of the chest and nightmares. In order to maintain two patients in a reasonable state of well-being they were later given neostigmine by mouth in addition to DFP. The amounts of neostigmine required were found to be one quarter or one half of those which had been required before DFP was given.

Little evidence was found of any correlation between the relief of symptoms produced by DFP and its inhibition of the activity of the blood-cholinesterases. Ninety to a hundred per cent. inhibition of the plasma pseudo-cholinesterase was maintained from the first day of treatment without any obvious change in symptoms. Inhibition of the red-cell true cholinesterase developed more gradually, and values of 40 to 50 per cent. of its activity before treatment were noted

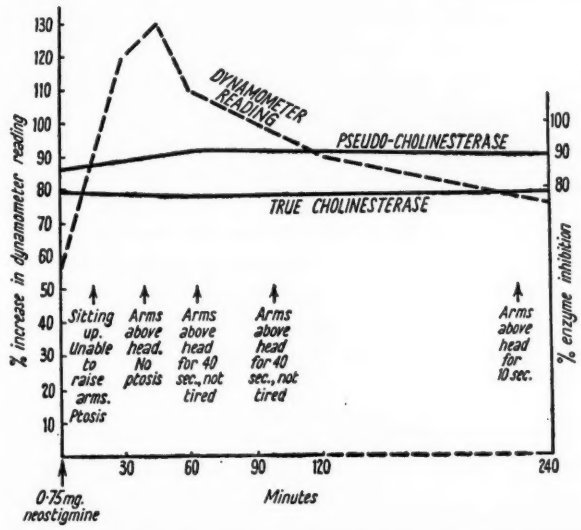
% increase in dynamometer reading
% enzyme inhibition
DYNAMOMETER READING
PSEUDO-CHOLINESTERASE
TRUE CHOLINESTERASE
Sitting up. Unable to raise arms. Ptosis
Arms above head. No ptosis
Arms above head for 40 sec., not tired
Arms above head for 40 sec., not tired
Arms above head for 10 sec.
0·75mg. neostigmine
Minutes

FIG. 4. The effects of a subcutaneous injection of neostigmine (0·75mg.) on the dynamometer readings and blood-cholinesterase levels of a myasthenic patient receiving daily doses of DFP. The neostigmine was administered 24 hours after the routine dose of DFP. The diagram shows the effects on plasma pseudo-cholinesterase and red-cell true cholinesterase activity, expressed as percentage inhibition, and on the dynamometer reading, expressed as percentage increase over the value prior to DFP treatment.

about the tenth or twelfth day, at about the same time as clinical improvement was observed. When higher ranges of inhibition (80 to 90 per cent.) were reached, various toxic symptoms occurred such as stiffness of the jaw muscles, fasciculations, and in one case generalized convulsions and delirium. These effects were controlled by temporary withdrawal of DFP, but their disappearance was not related to any appreciable change in red-cell cholinesterase activity. The general impression reached at this time was that, to procure the most satisfactory clinical effects, the range of inhibition for red-cell true cholinesterase should be 50 to 70 per cent. Later experience, however, showed that in some patients toxic effects occurred intermittently at lower levels of inhibition (40 to 50 per cent.), and that when a control solution without DFP was substituted, clinical improvement was still evident when the inhibition was only 10 to 30 per cent. On the other hand, severe signs of the disease were still present in two

patients (Cases 7 and 9) when the inhibition was 70 and 75 per cent respectively. During treatment with DFP tightness of the chest, disturbed sleep, and nightmares were intermittently reported, but were not related to the level of inhibition of blood-cholinesterase or to the absence of atropine therapy. The occurrence of fasciculations was usually, but not invariably, associated with high levels of inhibition. Electro-encephalographic records taken at these times showed a marked lowering of amplitude, with diminished alpha activity. The patients in question were all receiving atropine, 0·5 mg. twice daily, and this may have affected the records (Harvey, Lilienthal, Grob, Jones, and Talbot, 1947). Nausea, vomiting, and abdominal pain were rarely noted, no doubt owing to the administration of atropine (Rowntree, Nevin, and Wilson, 1950).

The effects of neostigmine in addition to DFP. When a single dose of neostigmine was given either by mouth or parenterally during DFP treatment, the patient always showed a clinical improvement which was more intense than that attained by DFP alone. This particularly applied to the relief of oculo-bulbar symptoms where these had not been affected by DFP. Fig. 4 shows the effect of an injection of 0·75 mg. of neostigmine on the dynamometer readings of a patient already receiving DFP. A marked increase in muscle strength occurred, with relief of ptosis, but there was no significant change in the red-cell cholinesterase activity.

Discussion

The primary aim of the work here reported was to use DFP as an agent for investigating the causation of myasthenia gravis. Its prolonged administration was intended to determine whether clinical improvement would result if sufficient time were given for the diffusion of DFP from the blood to the tissues. Whereas a single dose of DFP produced no particular effect if given intramuscularly, when injected into the brachial artery it restored muscle power and the pattern of the muscle action potential. This effect was localized to the injected arm, and led to the assumption that if the tissue concentration of DFP could be maintained at a sufficiently high level it might result in a change in the clinical condition of the patient. This assumption has been justified to a limited extent only. Some patients did not benefit from the prolonged administration of the drug, while in others only certain muscle groups were influenced; for example, the craniopharyngeal muscles were more resistant to change than the peripheral muscles. This limited effect of DFP is further illustrated by the fact that neostigmine, when given during prolonged treatment with DFP, produced a marked increase in the intensity and extent of clinical improvement. There is no doubt that DFP is not a suitable or reliable drug for the routine treatment of myasthenia gravis. It not only fails in small doses to relieve the signs and symptoms as effectively as neostigmine, but if administered in larger doses it produces the undesirable side effects already described without completely relieving the muscular weakness. The best that can be said for DFP as a therapeutic agent is that it may enable patients with weakness of the arms and legs to rise in the morning without a dose of neostigmine, but that it rarely

relieves the signs and symptoms sufficiently for neostigmine treatment to be entirely dispensed with. The limited experience we have gained in using DFP supplemented by neostigmine indicates that even if DFP is only given every third or fourth day, and the daily requirements of neostigmine thereby reduced by one-half or three-quarters, the clinical effect obtained scarcely justifies the extra measures involved in administering an oily solution.

It is clear that when clinical improvement was observed after DFP, it was not directly related to the degree of inhibition either of red-cell or of plasma cholinesterase activity. Nor were the effects produced by neostigmine, when given alone or in conjunction with DFP, related to the concurrent changes in plasma or red-cell cholinesterase activity. However, neither the inhibition of pseudocholinesterase in plasma nor that of true cholinesterase in red cells is necessarily a reliable index of the inhibition of cholinesterase at the neuromuscular junction. In this region the true cholinesterase normally responsible for the destruction of released acetylcholine is not confined to the nerve-endings, but occurs also at the motor end-plates; even degeneration of the motor nerves does not produce a decrease in the cholinesterase activity of the motor end-plates (Feng and Ting, 1938; Couteaux and Nachmansohn, 1938). Our observations give no indication of the inhibition of true cholinesterase activity in these regions. Experiments *in vitro* have shown that neostigmine and DFP produce comparable inhibitions of true cholinesterase activity in skeletal muscle (Wilson, Maw, and Geoghegan, 1951). If the clinical effects of these drugs are due to their anti-cholinesterase activity, a possible explanation of the differences of the clinical response to DFP and to neostigmine is that the two drugs differ in their ability to reach, and inhibit, the cholinesterase of the motor end-plates. This assumption would explain all our results, but we are unable to state which of the possible physicochemical factors, such as tissue permeability, are involved. The difference in availability of the two compounds at the motor end-plates may also be due to the fact that neostigmine combines reversibly with tissue-cholinesterase, while DFP does so irreversibly. Thus when neostigmine is distributed in the blood and tissues a certain proportion of uncombined neostigmine must always be present. In contrast, the stability of the complex formed between the enzyme and DFP is such that free DFP is presumably available only when high concentrations of the drug are used. In the case of DFP given intra-arterially in a high concentration, the effects were observed only in the injected arm, but it is possible that if a much higher concentration of the drug had been used, sufficient free DFP might have been available to produce corresponding effects in the non-injected arm. A further possibility which cannot yet be excluded is that the effects of neostigmine may be due to an action other than its anti-cholinesterase activity. Neostigmine, in contrast to DFP, has a direct action on skeletal muscle as demonstrated in the intact cat (Riker and Wescoe, 1946; Riker, Wescoe, Cattel, and Schorr, 1946) and in the isolated frog rectus preparation (Miquel, 1946). It would be interesting to know whether this acetylcholine-like action of neostigmine plays an important part in the relief of myasthenic symptoms.

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Summary

1. The effects of DFP and of neostigmine given by intramuscular and intra-arterial injection have been compared in patients with myasthenia gravis. The observations have demonstrated the difficulty of correlating the clinical effects with changes in the activity of the true and pseudo-cholinesterases of blood.

2. The clinical response produced by intramuscular injection of neostigmine was associated with only slight inhibition of the true cholinesterase of the red cells. In contrast to neostigmine, DFP produced no immediate clinical effects when injected intramuscularly, though it inhibited the activity of the pseudo-cholinesterase of plasma to a greater extent than neostigmine.

3. Action potentials of the small muscles of the hands were recorded. The muscles were fatigued by electrical stimulation of the nerves, and the effects of DFP and of neostigmine, injected into the artery of one arm, were observed in both hands. DFP restored the action potentials to the pre-fatigue state, but only on the injected side; the true cholinesterase activity of the venous blood from both arms was inhibited by about 20 per cent. The effect on the muscle action potential could be demonstrated for as long as four days after the injection. Neostigmine restored the muscle action potentials on both hands, but the effect lasted for about 80 minutes; the true cholinesterase activity of the venous blood was inhibited by about three per cent.

4. DFP was administered intramuscularly in small doses to 10 patients for periods varying from two weeks to two and a half years. The clinical effects and the changes in blood-cholinesterase activity are described. It is concluded that DFP is not a suitable or reliable drug for the routine treatment of myasthenia gravis, since it fails to relieve signs and symptoms as effectively and consistently as neostigmine.

5. The possible differences in the mode of action of the two drugs are discussed.

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A CONTRIBUTION TO THE PATHOLOGY OF SJÖGREN'S DISEASE[1]

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With Plates 7 to 10

Though the recognition of this disease is due to the investigations of an eye-specialist, Henrik Sjögren, of Jönköping (1933 and later), the eye lesion (keratoconjunctivitis sicca) need not be the presenting feature, and patients may first seek medical advice because of enlargement of salivary glands or because of xerostomia (Raffle, 1950). In its complete form Sjögren's disease includes keratoconjunctivitis sicca, xerostomia, rhinitis sicca, pharyngitis sicca, and laryngitis sicca, but incomplete forms are more often seen. The chronic inflammatory changes in the parotid glands, usually without suppuration but with recurrent exacerbations, tend to produce permanent enlargement, sclerosis, or atrophy, in irregular combination. Analogous changes occur in the other salivary glands, in the oral mucosal glands, and also, though usually without obvious clinical enlargement, in the lacrimal glands. It seems certain that many cases have been labelled Mikulicz's disease or Mikulicz's syndrome, and indeed according to old nomenclature all cases of Sjögren's disease in which there is any clinical enlargement of salivary glands, even without definite enlargement of the lacrimal glands, might be included amongst examples of Mikulicz's syndrome due to unknown pathogenic agents. The sweat glands of the skin and the acid-producing glands of the stomach may be involved. In the case about to be described the dryness of the bronchial mucosa played possibly the most disastrous part. The clinical onset, often more marked on one side than the other, is intermittent and insidious. The patients are mostly middle-aged women. Clinical accompaniments may include an accelerated blood-sedimentation rate, alterations in the blood count, body temperature and glucose-tolerance curve, and not rarely rheumatoid arthritis. Various non-ocular features may be found in addition to the changes in the salivary glands and mouth (Weber, 1945). According to Sjögren's investigations it seems clear that microscopical changes in the salivary and lacrimal glands precede the dryness of the mouth and eyes and obvious enlargement of salivary glands. The elaborate post-mortem histological examination in the case we here describe seems to confirm the view that the pathological basis of the dryness of the mucous membranes, and in some cases of the skin, consists in a chronic inflammatory atrophy

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of unknown causation involving the salivary, lacrimal, mucosal, and sweat glands. This pathological dryness may give rise to obstructions in the parotid and salivary glands and in the bronchial tubes, with consequent formation of secondary inflammatory granulomata and suppuration owing to the breakdown of the natural defensive mechanism.

Case Report (Ellman and Weber, 1949)

History (1948). The patient is a delicately built woman of medium height, aged 34 on November 13, 1948, thin, but apparently not losing weight. Her father died at 57 years of heart failure; he suffered from bronchitis. Her mother died at 69 years of 'sugar diabetes'. The parents had eight children, of whom the patient is the seventh; all the others are said to be living and healthy. The patient herself has always been thin and delicate-looking, and since the age of 13 years has been subject to short Raynaud-like attacks in the fingers—the tips turn white and then blue—relieved by putting the hands into hot water. She had measles at 17 and scarlet fever at 21 years. While still in the fever hospital after the scarlet fever she developed temporary swellings on both sides of the face, which were considered to be possibly mumps. About 1940 she noticed a peculiar dryness of the lips and mouth, which she did not get rid of. In January 1942 painless cherry-sized parotid swellings developed, one on each side, and were diagnosed as Mikulicz's disease. For these she received deep X-ray treatment at the Cancer Hospital (six séances) and they disappeared, but not the dryness of the mouth. Menstruation, which began at 12 years of age, has remained normal. She married in February 1939, and in December 1943 a boy child was delivered by caesarean section, which was performed owing to the presence of a uterine fibroid; this was removed at the same time. The boy was normal at birth, and has remained healthy. After suckling him for eight and a half months she developed two small painless lumps (September 1944) one on each side, under the lower jaw. With deep X-ray treatment (six séances) they disappeared. She received further deep X-ray treatment in February 1946, but for the past 18 months she has had a small painless swelling in the right sublingual region. About September 1944 her eyes felt hot, dry, and irritable, and a doctor told her she had conjunctivitis. It cleared up, but has returned on and off ever since. In April 1946 she suffered from 'dry pleurisy', first on one side and then on the other. For this she was in bed for three weeks only, but never got rid of the dry cough and since then has never felt quite well. Since then the eyes have been drier, and in February 1948 they became much worse and 'follicular' conjunctivitis was diagnosed. In May 1948 a stiff neck was followed by painful swelling in the knuckles, and pain and stiffness in the wrists, knees, feet, and left shoulder, with some fever. This polyarthritis of the rheumatoid arthritis type, for which she was referred to one of us (P. E.) by Dr. W. Edwards and treated at the Leatherhead Hospital, has now nearly subsided. Her dry cough has become much worse, and when she is talking she has to sip water frequently to relieve the dryness.

Present condition (1948). She complains of dryness of eyes, mouth, and throat, and an irritable dry cough, much worse on talking. Sometimes she has slight difficulty in swallowing. Most of her teeth have been extracted. By palpation with the finger and thumb a painless cherry-sized swelling can be felt below the tongue to the right of the middle line. There is slight symmetrical enlargement of the thyroid gland, but no clinical evidence of thyrotoxicosis.

A blood count on August 14, 1948, showed haemoglobin 98 per cent., erythrocytes 4,980,000 per c.mm., colour index 0·99, and leucocytes 6,000 per c.mm.

Another blood count on December 31 showed haemoglobin 103 per cent., erythrocytes 5,700,000 per c.mm., colour index 0·9, and leucocytes 7,600 per c.mm. (polymorphs 81 per cent., lymphocytes 18 per cent., monocytes 1 per cent.). The urine showed nothing abnormal. The blood-pressure was 120/80 mm.Hg. The blood Wassermann reaction was negative. The blood sedimentation-rate on June 28, 1948, was 5 mm., and on September 26, 22 mm., in one hour (normal 4 to 8 mm.). The blood-calcium was 10·6 mg. per 100 ml., blood-phosphorus 3·9 mg. per 100 ml., and blood alkaline phosphatase 9 units. There has been no sputum at present. There is no clinical evidence of disease of the heart, abdomen, or central nervous system. In the lungs there is diminution of air-entry at both bases, the breath sounds are tubular in type at the left base, and numerous dry crepitations can be heard at both bases, but are especially marked at the left base. X-ray examination of the chest on July 11, 1947, showed diminished translucency in the left lower lobe, with pleural involvement. On August 16, 1948, there was an area of consolidation in the left lower lobe, with some scattered opacities in the right lower lobe. The heart, mediastinum, and trachea were centrally placed, the left diaphragm was obscured, and the heart was normal in shape, size, and position. A further skiagram on November 30, 1948, showed little appreciable change. Bronchoscopy was negative, except for dryness of the bronchial mucosa; no secretion was obtained (Mr. W. P. Cleland, St. Helier Hospital, Carshalton). An electrocardiogram was normal. The hands showed soft-tissue swelling of the proximal interphalangeal joints, but no bony changes, nor were there any bony changes in the other joints. The following additional investigations were carried out at the Hammersmith Hospital. The sputum showed gram-positive cocci and diphtheroids on direct smear, and *Staphylococcus aureus* on culture. A fractional test meal gave a normal secretion of hydrochloric acid. The urinary excretion of 17-ketosteroids and the glucose-tolerance test were normal. Schirmer's lacrimation test showed moistening along 0·5 cm. of the filter paper, compared with 3 to 5 cm. in controls. A salivation test, consisting of the collection of saliva for three minutes after chewing and swallowing fruit, gave 0·8 ml., whereas control subjects produced 5 to 9 ml. A heating test for sweating gave a normal response. A liver biopsy, performed because pulmonary sarcoidosis had been suggested, showed normal histological structure.

Treatment (1948). Treatment was directed symptomatically to the dry eyes, dry mouth, and dry bronchial mucosa. So far as the eyes were concerned cod-liver oil drops gave symptomatic relief. Attempts were made to increase the salivary secretion by pilocarpine, mecholine, and physostigmine. These produced no appreciable response as shown by the salivation test. In the hope that the changes at the base of the left lung might be improved an attempt was made to alleviate dryness of the bronchial mucosa by keeping the patient for a fortnight in a steam tent. This had no beneficial effect on the respiratory condition, and the patient thought that the dampness aggravated the arthritis. Breathing exercises and postural drainage produced no significant result. She was given vitamin A, 150,000 units daily, empirically, as it was thought that this could not possibly do any harm and might conceivably do some good. Closure of the lacrimal ducts by local diathermy was not carried out, since the eye symptoms were not the most troublesome. The patient thinks that inhalation therapy helped her at the Hammersmith Hospital.

Subsequent History

At the end of March 1949 the patient developed a spontaneous pneumothorax on the right side, for which she was admitted as an emergency to Dorking County

Hospital under the care of one of us (P. E.). Subsequent to her admission on March 30 there were two recurrences of severe dyspnoeic symptoms. She was transferred on April 6, after consultation with Mr. W. P. Cleland, to the Chest Unit at St. Helier Hospital; she was then dyspnoeic and cyanosed, with signs of pneumothorax on the right side and a loud superficial crepitus at the left base. The liver was palpable two finger-breadths below the costal margin. Silver nitrate pleurodesis of the right lung was tried by Mr. Cleland on April 7, 1949. On thoracoscopy no adhesions were seen. The posterior and lateral aspects of the upper lobe seemed lobular and bullous; the rest of the lung appeared smooth. After the pleurodesis the course of the illness became stormy, with gradual adhesion of the pleural surface of the right lung and a general downhill trend. Signs of pleural involvement of the left lung remained present from the time of her admission. Signs of consolidation developed later in the left lung. From April 1949 oxygen inhalation was needed with increasing frequency. The blood-pressure, which had been 100/70 on her admission, dropped to 95/65, and the picture became one of circulatory failure with cold extremities, dyspnoea, tachycardia, and cyanosis. The patient was given ouabain gr. 1/250 three times a day and placed in an oxygen tent. This resulted in considerable improvement for a few days, after which there was rapid deterioration and life appeared to be maintained mainly by the oxygen tent. On June 12, 1949, she collapsed and died.

The results of the most recent investigations were as follows. *April 6, 1949*: a blood count showed erythrocytes 4,570,000 per c.mm., haemoglobin 77 per cent., colour index 0·85, and leucocytes 10,700 per c.mm. (polymorphs 84 per cent., eosinophils 1 per cent., basophils 1 per cent., lymphocytes 10 per cent., monocytes 4 per cent.). *May 10*: the blood-urea was 15 mg. per 100 ml., the serum-calcium 16·4 mg., and serum-protein 5·5 mg. per 100 ml. *May 25*: a catheter specimen of urine was acid in reaction and contained a trace of protein. The deposit consisted of a few hyaline, granular, and cellular casts, leucocytes, and calcium oxalate crystals. The urine was sterile on culture. *June 11*: a catheter specimen of urine was acid in reaction and contained a trace of protein. The deposit consisted of a few hyaline casts and leucocytes, and a moderate number of calcium oxalate crystals, and the urine was sterile on culture. An electrocardiogram showed inversion of the T-wave in leads II and III. Both corneae showed punctate staining with fluorescein. The left eye showed filamentary epithelial shreds. The filter-paper test showed almost total xerophthalmia in the right eye. A corneal ulcer was present on the right side.

Post-mortem Report (Dr. T. E. W. Goodier)

External appearances. The body was that of a thin, asthenic, young adult, brunette female. A healed left paramedian operation scar was present on the lower abdominal wall. The conjunctivae were slightly roughened, but their vessels did not appear injected.

Internal appearances. Dissection of the orbits and of the parotid and submaxillary region revealed no visible lacrimal or salivary glandular tissue. Scraps of fibrous tissue only were found. The mucous membrane of the nose, nasal sinuses, nasopharynx, pharynx, and mouth appeared normal, stripped comparatively easily, and did not appear fibrotic. The tonsils were small. The brain and other cranial contents were normal.

Neck. The thyroid gland appeared normal. There were a number of enlarged, soft, discrete lymph-nodes in the right cervical and right tracheo-bronchial chains. No thymus tissue was visible.

Chest. The trachea and bronchi were full of almost colourless frothy fluid. Their mucous membranes were slightly injected, but otherwise macroscopically normal. The right pleural cavity was completely obliterated by a quarter-inch layer of gelatinous adhesions. The right lung showed a uniform massive oedema, with early bronchopneumonic changes at the base. No other pathological changes were visible. The left pleural cavity contained a few ounces of free fluid over the diaphragm, and a loculated network of fibrous adhesions above. The loculi contained air, and on an average measured one inch in diameter. The left lung showed a collapsed, fibrotic base, otherwise merely a massive oedema like that in the right lung. The heart was a well-developed 'cor pulmonale'. The right side showed hypertrophy and dilatation, and the pulmonary artery was dilated. The pericardial cavity contained nearly half a pint of opalescent, straw-coloured fluid. The endocardium appeared normal.

Abdomen. The gastro-intestinal tract, liver, spleen, and suprarenals were normal. The pancreas was congested and showed multiple petechial haemorrhages. Its consistency was normal to the touch. The kidneys were normal, but there was slight injection of the ureters and bladder. The uterus was of the size of a fist owing to multiple grape-sized 'fibroids'. A well-healed caesarean scar was present. The tubes and ovaries appeared normal.

Extremities. Dissection of the knee-joints showed no synovitis and no periarticular thickening.

Comment. The cause of death appeared to be acute pulmonary oedema due to left-sided failure of the heart, the right side of which was already strained by the sequelae of bilateral spontaneous pneumothorax.

Histological report.

Pineal gland, and *pars anterior of pituitary gland.* No gross abnormality.

Left lacrimal gland and *conjunctiva of superior fornix.* The glandular acini have been replaced by a collection of small round cells in a fibrous scar-tissue matrix. The scar is well organized, containing thick-walled blood-vessels. Numerous small round cells are also seen just beneath the squamous epithelium of the superior fornix. They show a tendency to focal arrangement, as in the so-called follicular conjunctivitis.

Right lacrimal gland. This again consists mainly of lymphocytes, together with a few plasma cells, histiocytes, and fibroblasts, in vascular scar-tissue. A small number of degenerate serous acini and ducts containing inspissated acidophil material are the only remains of normal lacrimal tissue (Plate 7, Fig. 1).

Left parotid gland. Mainly replaced by fat and scar-tissue. Only a few foci of collapsed, partially necrotic serous acini, and scarred, somewhat dilated ducts containing cellular and amorphous debris remain to indicate the site of the gland, and each focus is infiltrated and surrounded by small round cells (Plate 7, Fig. 2).

Right parotid gland. This consists of a few degenerate serous acini and dilated ducts embedded in a chronic inflammatory exudate. The whole mass occupies less than a tenth of the volume of the normal gland.

Pillar of fauces. There is a little degeneration and some thickening of the squamous epithelium. The submucosa contains a few degenerate and dilated mucous ducts, with a mild chronic inflammatory exudate. No normal mucous glands are seen.

Faucial tonsils. There is chronic inflammation and reactive hyperplasia.

Right sublingual swelling. A circumscribed, encapsuled mass of scarred lymphoid tissue. Chronic inflammatory changes are marked, and some old, pigment-bearing histiocytes are present. In one area beneath the 'capsule' a

solitary ductule containing acidophil debris has been cut across (Plate 9, Fig. 5).

Buccal mucosa. The epithelium is slightly thicker than normal and shows a tendency to keratosis. The submucosa contains thick-walled capillaries and a mild chronic inflammatory exudate, but mucous glands are absent.

Tongue (posterior third). No taste-buds are seen. The lamina propria contains a chronic inflammatory exudate consisting mainly of lymphocytes, with a smaller number of histiocytes, plasma cells, and polymorphs (Plate 8, Fig. 3). Few von Ebner's (serous) glands are visible; they show advanced atrophy and cellular infiltration (Plate 8, Fig. 4). The groups of mucinous glands seen are degenerate and their dilated, tortuous ducts show chronic inflammatory changes.

Cervical lymph-nodes (right side). These show chronic inflammatory activity consisting of dilatation and commencing fibrosis of the sinuses, plasma-cell exudate, and vascular congestion.

Nasal mucosa. Goblet cells are numerous and distended with granular mucus. The mixed glands in the submucosa are somewhat atrophic, and the lumina of their ducts and acini contain inspissated mucus. The submucosa contains an exudate which is more acutely inflammatory than the exudates so far seen.

Nasopharyngeal mucosa. The epithelium appears normal, but the submucous glands are atrophic, with disorganization of their cellular arrangement and only traces of mucus visible. The glands are loosely infiltrated by a chronic inflammatory exudate, and some fibrosis has occurred.

Epiglottis. The epithelium appears normal. The mixed mucous glands in the submucosa of the posterior aspect have their architecture moderately well preserved, but the acini are necrotic, the ducts are dilated and contain granular mucus and desquamated mucous cells, and there is interstitial chronic inflammatory infiltration.

Glottis. The epithelium is normal except for mild chronic inflammatory changes. The architecture of the mucous glands is good, but there is an inflammatory infiltration and degeneration of acinar cells. Serous cells are especially granular, and mucous cells have necrotized and fused, leading to obliteration of acinar lumina. The thyro-arytenoid muscle appears degenerate and oedematous.

Thyroid gland. The pyramidal and lateral lobes are normal except for some colloid hyperplasia.

Trachea. The pseudostratified ciliated columnar epithelium is normal and contains numerous goblet cells. The mixed glands of the lamina propria are scanty, and those present are degenerate, with fragmentation of their cytoplasm and obliteration of their lumina.

Bronchus (*large cartilaginous type*). The epithelium comprises numerous goblet cells containing granular mucus, but no submucous glands are seen.

Base of left lung. The pleura is much thickened, and consists externally of oedematous connective tissue, and internally of a denser vascularized scar-tissue in which chronic inflammatory foci of small round cells are seen. The lung shows collapse, with much scarring and some emphysema. There is considerable low-grade chronic inflammation and a superimposed acute bronchopneumonia, alveoli being filled mainly with histiocytes and bronchioles with pus, 'dust-cells', and desquamated, disorganized mucous epithelium. Gram's stain reveals gram-positive cocci only.

Middle lobe of right lung. There is marked oedema, with congestion and some bronchopneumonia. There is also old fibrotic scarring and emphysema. The larger bronchioles are deficient in epithelium, which in some cases still lies desquamated in the middle of the lumen, and in places oedematous fibro-granulation tissue lines the bronchiole. Alveoli show oedema and granular

material, many histiocytes, some blood- and a few pus-cells. Small interstitial foci of lymphocytes are common.

Upper and middle lobes of right lung. A large section (compare Plate 10, Fig. 7), shows changes similar to those described above. There is no evidence of focal granulomata.

Pleura of right lung. This has become a layer, 1 cm. thick, of oedematous fibro-granulation tissue.

The *right tracheo-bronchial lymph-nodes* show extreme sinus-catarrh. Blood- and pus-cells as well as histiocytes are seen in the sinuses.

Skin of right upper arm. The numerous sweat glands show atrophic changes, with closing lumina and lymphocytic and plasma-cell infiltration (Plate 9, Fig. 6).

Anterior cruciate ligament of right knee. Collagen fibres are somewhat hyaline, but the synovia appears normal.

Oesophagus. Appears normal except that no submucosal glands are apparent.

Stomach (fundus). Goblet cells in the necks of the gastric glands are distended with much mucin, and the slight degenerative changes in the glands themselves are more marked in the zymogen than the parietal cells. An excess of small round cells is present in the lamina propria.

Ileum. The lumen contains much mucinous debris and necrotic villous cells. The crypt cells are necrotizing, but have produced much mucin. A Peyer's patch is seen to be hyperplastic and scarred.

Colon. Much 'foamy' mucin production has taken place in the goblet cells of the somewhat necrotic crypts.

Liver. There is dilatation of the lymph spaces between the hepatic cells and the reticular fibres of the sinusoidal lining cells; otherwise appearances are within normal limits.

Pancreas. Has undergone complete post-mortem autolysis.

Spleen. There is some congestion; the appearances otherwise are within normal limits.

Kidney. Glomeruli show slight thickening of the capillary basement-membrane, and there is some swelling and necrosis of tubule cells, probably due to post-mortem autolysis. There is also vascular congestion.

Left ovary and Fallopian tube. There is no gross abnormality.

Fundus uteri. The endometrium is post-menstrual and is within normal limits. The more cystic of the glands of the basal layer still contain mucin.

Cervix uteri. Nabothian follicles are filled with faintly acidophil granular mucus.

Vaginal mucosa (lateral wall). The squamous epithelium is atrophic in places, and roughened by tiny multiple inflammatory papillomatous projections with dilated capillaries. The picture resembles that of so-called 'granular vaginitis'.

Conclusion. The appearances are compatible with Sjögren's disease. Death was due to acute bronchopneumonia.

Report on 36 Sections stained with Haematoxylin and Biebrich Scarlet

(Professor Dorothy S. Russell)

The significant histological changes are remarkably uniform and affect the left and right lacrimal glands, the left parotid (section of right not received) and the right sublingual glands. In addition the following mucosae and their subjacent secretory glands require mention: conjunctival, buccal, tongue, nasal and nasopharyngeal, pillar of fauces, epiglottis, larynx, trachea, bronchi, and oesophagus. The skin also shows related changes.

The *lacrimal glands* are replaced by more or less dense but poorly defined aggregates of small lymphocytes, penetrated by a few small blood-vessels, the walls of which are thickened by hyaline connective tissue. There is sclerosis of the fibro-adipose tissue throughout the sections. No residue of the lacrimal gland is present on the left; on the right two ducts, lined with low cuboidal epithelium and distended with hyaline acidophil material, remain (Plate 7, Fig. 1). An atrophied acinus is intimately related to one of these ducts. Conjunctiva is included in the specimen from the left; its epithelium is intact, but the lamina propria is infiltrated with lymphocytes and plasma cells. Two subjacent glands of Moll are atrophied and enveloped by lymphocytes.

The *left parotid gland* is represented by scattered groups of atrophied acini and ductules, the latter being dilated. All are surrounded by lymphocytes and a moderate number of plasma cells (Plate 7, Fig. 2).

The *right sublingual nodule* is presumably the remains of the salivary gland, which is now represented by a single tubule, with acidophil content and lined with low cuboidal epithelium (Plate 9, Fig. 5). The nodule is otherwise composed of small lymphocytes and a few larger cells which appear to be fibrocytes. There is hyalinization of the included blood-vessels, and a good deal of hyaline connective tissue surrounds the nodule.

The changes in the *mucosae* can be summarized as follows: there is diffuse infiltration of the lamina propria with small lymphocytes, plasma cells, and occasional neutrophil leucocytes, which is greatest in the nasal mucosa and tongue (Plate 8, Fig. 3) and less severe in the conjunctival, buccal, pharyngeal, laryngeal, and oesophageal mucosae. The epithelium of the tongue is in places atrophic. The ciliated epithelium of the nose, trachea, and bronchus is intact, and the normal complement of mucous goblet cells appears to be present. In all these regions there is a great reduction in the size and number of the *mixed* submucous glands and, in the conjunctiva, of the subconjunctival glands of Moll, and those present show all stages of degeneration and atrophy, with associated lymphocytic and plasma-cell infiltration (Plate 8, Fig. 4). Their ducts are frequently dilated and contain acidophil coagulum or debris. Occasionally their lining epithelium has undergone focal squamous metaplasia, e.g. in the fauces; elsewhere it is usually flattened. The connective tissues between these submucous glands show, in places, conspicuous mucinous alteration; this change is present in the tongue and larynx. There are no submucous glands in the specimen of buccal mucosa.

The *faucial tonsil* shows no significant changes beyond an excess of plasma cells in the lamina propria beneath the epithelium.

The *right cervical* and *paratracheal bronchial lymphnodes* show a non-specific reactive inflammatory hyperplasia. There is an excess of plasma cells, with occasional eosinophil leucocytes, in both cortex and medullary cords, in addition to the usual sinus-catarrh and enlargement of the follicles.

Lungs. Organized fibrous pleurisy is accompanied by engorgement and focal haemorrhages in all areas of the lung-tissue, and stages of a progressive organizing bronchopneumonia. The latter is most advanced at the 'left base' (of the lower lobe) where there is great fibrosis and collapse. In this region a large bronchiole shows focal squamous metaplasia of the epithelium. The pulmonary arteries appear normal. There is considerable focal lymphocytic infiltration, especially in the peribronchial connective tissues. In the right middle lobe there are a great many foamy macrophages in the alveolar spaces, differing from similar macrophages in other parts which contain the pigment characteristic of heart-failure.

Skin. The only obvious change is a selective inflammatory infiltration of the

stroma of the sweat glands with lymphocytes and a few plasma cells. There is considerable degeneration and atrophy of the epithelium of these glands (Plate 9, Fig. 6).

Sections of the acid-secreting part of the stomach, the ileum, and colon show no histological abnormality. The pancreas is completely autolysed. The kidney, spleen, and liver show back-pressure congestion, with parenchymal atrophy in the liver. The thyroid, pineal, and pituitary glands are normal. There are no significant changes in the genital tract, nor in the anterior cruciate ligament of the knee-joint.

Comment. The selective inflammatory involvement, with degeneration and atrophy, of the salivary and lacrimal glands, of the submucous glands throughout the respiratory and upper alimentary tract including the oesophagus, and of the sweat glands of the skin, suggests a unique disease. There is no evidence from these sections as to the nature of the agent responsible for the inflammation. The pulmonary changes may be interpreted as a secondary development, doubtless promoted by the absence of normal secretions from the tracheal and bronchial mucosae. The appearances in the right middle lobe are strongly suggestive of a lipoid pneumonia, which would be explained if the patient had been in the habit of using an oily medicament[2] for the lubrication of the upper respiratory passages. It is probable that the chronic inflammatory infiltration of the lamina propria of the various mucosae mentioned is again a secondary manifestation. From the histological appearances I should attribute death in this case to right heart failure supervening on cor pulmonale.—(*Signed*) Dorothy S. Russell, April 11, 1950.

Discussion

The elaborate study of this severe and progressive case of Sjögren's disease seems to confirm the view already expressed at the commencement of this paper, that the pathological basis of the dryness of the mucous membranes and skin consists in a chronic inflammatory atrophy of unknown causation involving the salivary, lacrimal, mucosal, and sweat glands. This pathological dryness may give rise to obstructions in the parotid and salivary glands and in the bronchial tubes, leading to a secondary inflammatory granulomatous process and suppuration owing to the breakdown of the natural defensive mechanism. It is worth while asking why the affected lacrimal glands in Sjögren's disease appear never to be clinically enlarged, although such enlargement has occurred in some cases regarded as Mikulicz's disease or Mikulicz's syndrome. Another remarkable point is that ozaena, though apt, especially in women, to accompany atrophic rhinitis, seems to be absent in Sjögren's disease. The present report appears to contain the most complete histological examination of a case of Sjögren's disease yet published. It would be out of place here to discuss the rarer phenomena which have been recorded in association with Sjögren's disease, or to endeavour to explain the fact that most of the patients are women (Weber, 1945). As to the association of the disease with rheumatoid arthritis, it should be remembered that rheumatoid arthritis is fairly common among women, and that very few patients with rheumatoid arthritis ever manifest any symptoms resembling Sjögren's disease. Various

[2] Cod-liver oil eye drops were given, but it appears that the patient also used oily nasal drops.

conditions of temporary dryness of the oral mucosa—e.g. in infections such as typhoid fever—may favour the development of secondary parotitis. Perhaps the occasional occurrence of sarcoidosis following symptoms suggesting Sjögren's disease may be explained in this way.

Lipoid pneumonia. There seems to be no doubt that the patient used an oily medicament against the dryness in her nose. Whatever part this remedy may have played in her fatal illness, the fact should be remembered in the treatment of future cases.

It is our pleasant duty to thank Professor Russell for her histological report, for her selection of the slides for illustration, and for valuable suggestions as to the pathological description of the case. We are also indebted to Mr. W. P. Cleland and his colleagues of the Chest Unit at St. Helier Hospital for their help and co-operation.

Summary

A case of Sjögren's disease is described with elaborate post-mortem, especially histological, examination. The pathological basis of the main clinical features (dryness of the mucous membranes and sometimes of the skin) consists in a chronic inflammatory atrophy of unknown causation involving the salivary, mucosal, and sweat glands. The pathological dryness may give rise to obstructions in the parotid and salivary glands and in the bronchial tubes, resulting in a secondary inflammatory granulomatous process and possibly suppuration.

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Note. We have not referred to the important French literature dealing with the subject. The omission does not affect our present contribution, which is mainly pathological, but there can be no doubt of the clinical and especially symptomatological value of the French papers. The disease or syndrome has sometimes been termed the Gougerot–Sjögren syndrome on account of Henri Gougerot's pioneer, but little known, paper in the *Bull. de la Soc. française de derm. et de syph.* (Paris, 1925), **32**, 376, which is headed 'Insuffisance progressive et atrophie des glandes salivaires et muqueuses de la bouche, des conjonctives (et parfois des muqueuses nasale, laryngée, vulvaire). "Sécheresse" de la bouche, des conjonctives', &c. Compare 'La Kérato-conjonctivite sèche de Gougerot–Sjögren', by Appelmans in *Arch. d'ophtalmologie* (Paris, 1948), New Series **8**, 577, and the numerous references given by A. Aimes, *Maladies et syndromes rares ou peu connus* (Paris, 2nd ed. 1950), p. 149.

FIG. 1. Right lacrimal gland. The remnant of the gland is surrounded by lymphocytes. The duct is distended with acidophil material (× 160)

FIG. 2. Left parotid gland. Nodule of gland showing atrophy and chronic inflammatory infiltration (× 160)

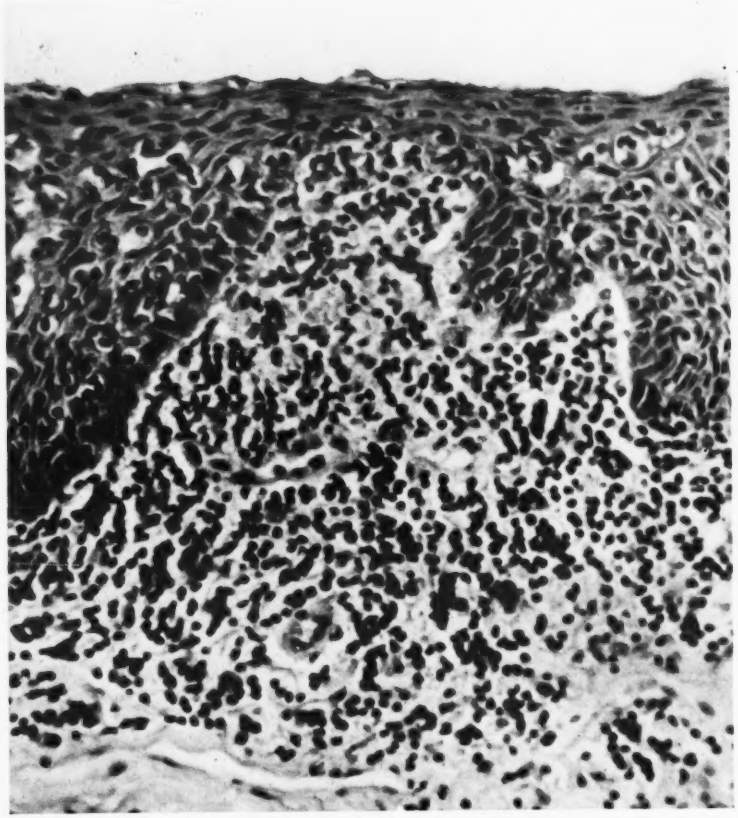

FIG. 3. Tongue (superficial). Area of chronic atrophic glossitis (× 300)

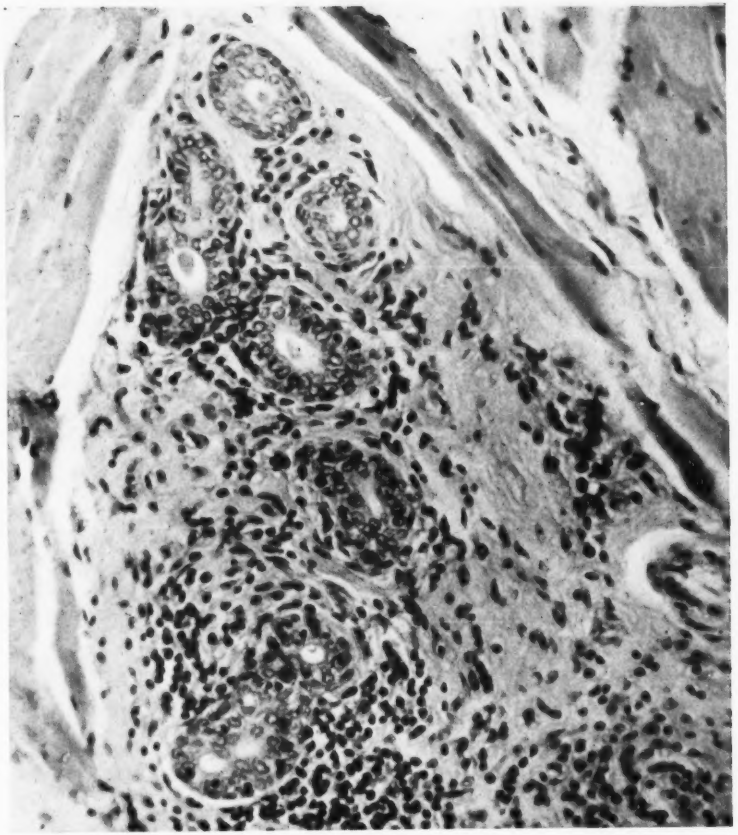

FIG. 4. Tongue (deeper). Group of atrophic glands with round-cell infiltration (× 280)

FIG. 6. Skin of upper arm. Atrophic sweat-gland with round-cell infiltration (× 120)

FIG. 5. Right sublingual swelling. Single ductule containing acidophil material and surrounded by round cells (× 1,000)

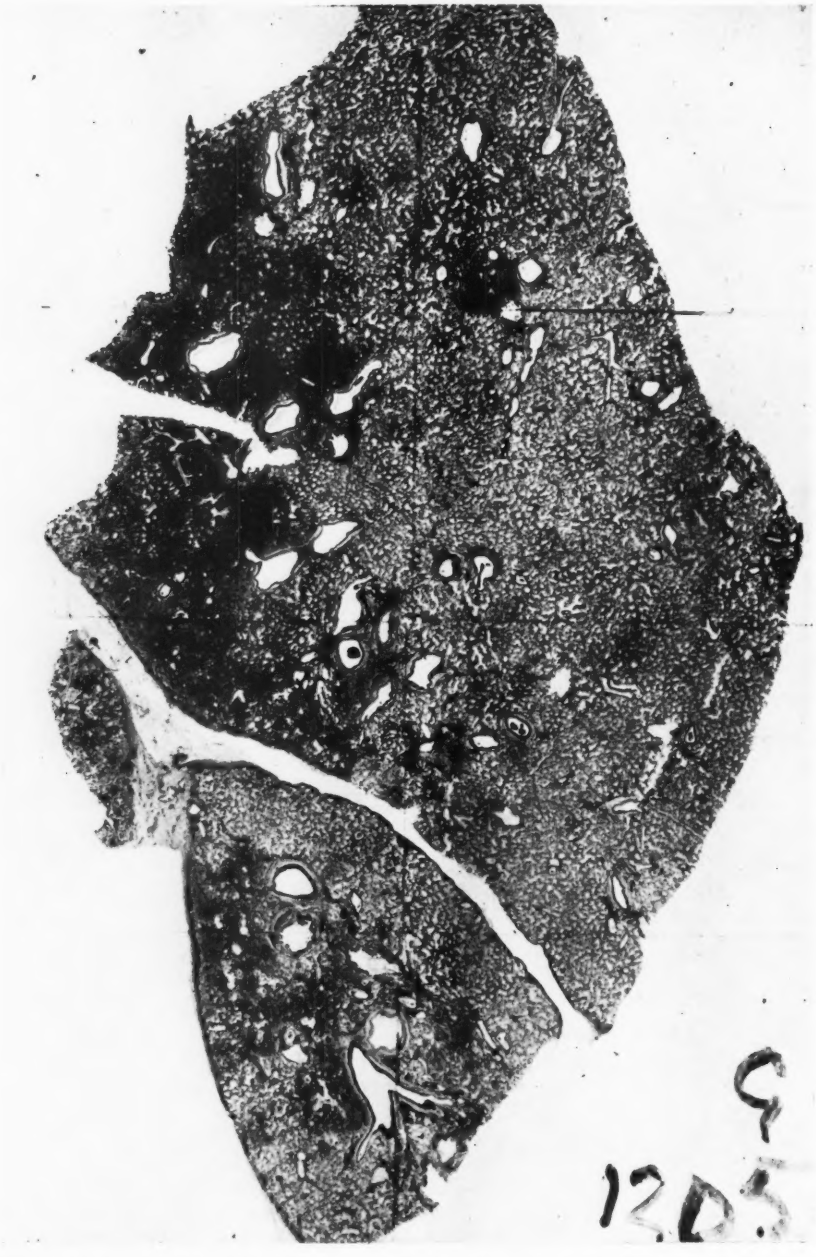

FIG. 7. Upper and middle lobes of right lung; sagittal section. The darker areas, mainly posterior, are bronchopneumonia. (× 2)

616.24–002–022.7 (Staphylococcus)

PRIMARY STAPHYLOCOCCAL PNEUMONIA[1]

By M. O. J. GIBSON and J. R. BELCHER

(From the London Chest Hospital)

With Plates 11 to 15

With certain qualifications, infections of the lungs due to *Staphylococcus aureus* may be divided into primary and secondary staphylococcal pneumonias. From an initial staphylococcal focus, most commonly situated in the skin, there may arise from time to time septicaemia or pyaemia. In this blood-stream infection the renal cortex, brain, bone-marrow, previously damaged heart valves, and lungs are the most frequent sites of localization. Such a haematogenous involvement of the lungs is a true secondary pneumonia, and since it is properly considered under the title of staphylococcal septicaemia, of which it is but one facet, it will not be further mentioned in this paper. The disease should be termed primary when it is the first manifestation of a staphylococcal infection in the body. Though it may possibly attack previously healthy people, it is most commonly found to affect those with a pre-existing lung disease or those who are suffering from influenza. In a sense, therefore, this second type of staphylococcal pneumonia is also secondary in many, if not in all, cases. But in order to differentiate it from the first or metastatic type of pulmonary disease the term primary appears to be justifiable. This paper is chiefly concerned with cases of primary staphylococcal pneumonia arising as a complication of influenza.

Incidence

In his monograph on influenza written in 1896 Leichtenstern drew attention to the frequency with which the pneumonia complicating this infection terminated in abscess formation. He had in 1890 reported seven such cases, all occurring in children under eight years of age. Netter (1892), in a carefully recorded bacteriological study of 95 cases of bronchopneumonia which came to autopsy, found that from the lungs of eight patients *Staphylococcus aureus* grew in pure culture. Though struck by the relative rarity of staphylococcal pneumonia, since the organism was so frequently found in the normal throat, he concluded that the body must be best prepared for the struggle against invasion by the bacteria which it normally harbours. Fraenkel in 1904 isolated the staphylococcus in pure culture directly from the lung of a fatal case in which the symptoms had been characteristic of staphylococcal pneumonia. The disease is more prevalent as a complication of epidemic influenza, but even so is uncommon. Chickering and Park (1919) emphasized its rarity by recording that in a series of 800 cases of pneumonia treated at the Hospital of the Rockefeller Institute, New

[1] Received August 28, 1950.

York City, between 1913 and 1918, only 13 were due to the staphylococcus, that is 1·6 per cent. Reimann (1933), reviewing the literature of 730 cases of pneumonia of other than lobar distribution, found that between 7 and 9 per cent. were due to staphylococci. Heffron (1939) analysed 3,319 cases of 'lobar' pneumonia, and found that only six were staphylococcal. He observed, 'It is not clear, however, that this organism can cause true lobar pneumonia, and the lesion produced is usually of the bronchopneumonia type'. Staphylococcal pneumonia in epidemic form was reported by Chickering and Park (1919) when it occurred at an American military camp in Columbia during the 1918 influenza pandemic. During the space of one month in the autumn of 1918, 8,100 patients with influenza were admitted to hospital. The majority made a rapid and uneventful recovery during the space of a few days, but 1,409 developed pneumonia. Of the 385 who died, the *Staphylococcus aureus* was grown from lung puncture *post mortem* in pure or nearly pure culture in 153 cases. The writers stress the fact that, as lung cultures were only obtained from 312 of the 385 fatal cases, it is reasonable to suppose that this number does not represent the total mortality due to the staphylococcus. The 11 per cent. incidence which they record of pneumonias of staphylococcal aetiology is therefore in all probability an underestimate. In a study of 58 patients with influenza admitted to the Hammersmith Hospital between December 1936 and January 1937, Scadding (1937) found 19 to have pulmonary consolidation. From two of these cases *Staphylococcus aureus* was grown as the predominant organism. One patient recovered, but the other, a girl of 16 years, died rapidly of a fulminating pneumonia identical in all respects with the disease described by Chickering and Park. Gáspár (1941) reported as due to the staphylococcus 38 out of 144 cases of all types of pneumonia examined *post mortem* over a seven-year period (1933–9). He noted that these cases usually followed an upper respiratory infection, and that two-thirds occurred during the first decade of life. In the extensive influenza epidemic during the winter of 1940–1 Finland, Peterson, and Strauss (1942) treated 66 cases of staphylococcal pneumonia. They remarked that the influenza itself was mild. At the same time Michael (1942) reported a further five cases from another hospital in Boston.

Primary staphylococcal pneumonia when not preceded by influenza is predominantly a disease of children, and is commoner in the neonatal period than at any other time of life. Smith (1935) and Dickie (1938) both reported outbreaks among infants in a maternity hospital. All the babies were well developed and apparently healthy. The source of infection was traced to throat carriers among the nursing staff or to infected milk from mothers who had breast abscesses. Macgregor (1936) encountered 10 cases between August 1935 and May 1936, and stressed the absence of any influenza epidemic during that period. The ages of his patients ranged from 16 days to three and a half years. Four had a preceding pharyngitis, and in one case aspiration of milk was the probable source of infection. Kanof, Kramer, and Carnes (1939) recorded 23 cases among children, and 16 occurred under one year of age. The disease showed the same seasonal incidence as pneumococcal pneumonia, occurring usually during the winter and

early spring. They noticed that a short upper respiratory infection commonly heralded the onset of pneumonia. Anspach (1947) made an interesting observation. He found that in 32 out of 33 autopsies of cases of fibrocystic disease of the pancreas, staphylococcal pneumonia was the immediate cause of death. Dickey (1950) had a somewhat similar experience, for in seven of the 10 cases of pancreatic cystic fibrosis seen by him over a seven-year period, a coagulase-positive *Staphylococcus aureus* was grown from the sputum. In the discussion following the reading of Dickey's paper, Schwachman stated that *Staphylococcus aureus* had been recovered from the nasopharynx in nearly all the 150 cases of cystic fibrosis of the pancreas studied by Foley and himself. Perhaps the experimental work of Stiner (1929) has some bearing upon the relationship of these two conditions. In guinea-pigs fed on a diet grossly deficient in all vitamins he observed the occurrence of pneumonia which was invariably due to *Staphylococcus aureus* or *Staphylococcus albus*.

Mortality

All writers have emphasized the high mortality in staphylococcal pneumonia. Thirteen cases were seen at the Rockefeller Institute Hospital during the first world war, and 10 of the patients died. Chickering and Park (1919), in the largest series on record, reported a 99 per cent. mortality, for only two of their 155 patients recovered. Among cases observed in the 1940–1 influenza epidemic in America, Finland, Peterson, and Strauss (1942) reported a 32 per cent. mortality, but only seven of their 66 cases had the fulminating quality of the 155 described by Chickering and Park. These seven patients all died. Brock (1945) in his *Studies in Lung Abscess* recorded a 20 per cent. mortality, for of his 30 patients with staphylococcal pneumonia encountered over a 12-year period six died. In assessing the death-rate of this infection the fulminating variety must clearly be differentiated from the less malignant and more chronic type. The former is as yet uninfluenced by treatment, whereas the latter is greatly benefited by modern therapy. The prognosis is worse in children than in adults, and the disease is especially lethal during infancy. Smith (1935), Macgregor (1936), and Clemens and Weens (1942) together reported 20 cases, all of which were fatal, in children under four years of age. Kanof, Kramer, and Carnes (1939) reported a reduction of mortality to 65 per cent. in their 23 primary cases in children; 16 of these patients were less than one year old. In the series described by Blumenthal and Neuhof (1946) 14 out of 40 children died (35 per cent. mortality), and all the fatal cases were fulminating in character and presented an acute diffuse pulmonary suppuration. Of the 10 patients described in detail in the present paper, all recovered; but none were young children and, though some were gravely ill, none showed the clinical picture of overwhelming infection described by Chickering and Park.

Clinical Features

A. *Fulminating pneumonia*

Apart from some of the sporadic cases occurring in infants, the fulminating and frequently fatal variety of the disease is almost confined to major influenza

epidemics. Chickering and Park (1919) observed in their cases that after three to four days of typical influenza the patient's condition became critical. The picture was one of septicaemia with severe prostration, anxious facies, and a curious cherry-red-indigo-blue cyanosis at a time when physical signs of pulmonary involvement were scanty. An initial rigor, pleural pain, and subsequent herpes or delirium were rarely encountered, nor was sweating a striking symptom. The high fever was associated with a relatively slow pulse. A characteristic salmon-pink purulent sputum was noted in most cases. Leucopenia was common. Complications were rare, for death usually supervened before these had time to develop. Of their 155 patients, of whom only two recovered, 85 had died by the tenth day of the disease.

B. *Acute pneumonia*

1. *Symptoms.* In epidemics of influenza since that of 1918–19 staphylococcal pneumonia, though frequently acute and alarming, has appeared more often as a less virulent disease. This modified clinical picture has been our experience and, though many of our patients were gravely ill, none has shown a fulminating infection. The patient is taken ill with what appears to be an ordinary attack of influenza. Instead of the normal spontaneous improvement after two or three days, the malaise, pyrexia, and dry cough persist. After a period of one to two weeks, during which there is a singular absence of localizing signs, the patient becomes more ill and complains, in most cases, of a pleuritic pain. Dyspnoea develops, and sometimes cyanosis. His cough becomes productive. The purulent odourless sputum may be pinkish or frankly blood-stained; though small in quantity at first, it rapidly increases to several ounces a day and may continue at this level for many weeks. In milder cases which resolve without radiologically visible abscess formation the quantity of sputum is considerably less. Even the so-called 'sporadic' cases frequently have a mild upper respiratory tract infection for two to three days before pulmonary symptoms appear.

2. *Physical signs.* The physical signs in the chest vary greatly in character and in location. Sometimes the bronchial breathing, whispering pectriloquy, and bronchophony of lobar consolidation can be detected, but more often the signs are those of localized areas of deficient air entry with crepitations. A pleural rub can often be heard at the onset, and the signs of fluid, or of air above fluid, in one or both pleural cavities may be discovered later in the illness. The pulse-rate remains slow compared with the temperature, but suddenly increases if a pulmonary abscess ruptures into a pleural cavity—a not infrequent occurrence.

3. *Empyema.* In adults the recorded incidence of empyema varies from 10 to 30 per cent. In children pus will be found in the pleural cavities in about 50 per cent. of cases. Only four of our 10 cases developed this complication, but none of our patients was under 14 years of age. Pyopneumothorax, rarely seen in adults, is a relatively common occurrence in young children, and is the major factor in the high death-rate in this age-group, the prognosis being little altered by any form of treatment. The diagnosis of a tension pyopneumothorax from

a distended lung abscess may be very difficult, but is of no great moment so far as treatment is concerned.

4. *Course.* The general condition of the patient usually improves rapidly, the dyspnoea, cyanosis, and pleural pain disappearing and the temperature falling to normal within the first week. Thereafter small spikes of pyrexia may recur, associated with temporary occlusion of a bronchus communicating with an abscess cavity. But in spite of the satisfactory response which can be inferred from rapid clinical improvement and from the sensitivity of the staphylococcus to penicillin *in vitro*, the productive cough may continue for many weeks, and the time before radiological resolution is complete may be four months.

5. *Blood culture and count.* In the primary disease, in contrast to secondary staphylococcal pneumonia, a positive blood culture is seldom obtained, and the development of a metastatic abscess is uncommon except in the few patients who are left with a chronic suppurative pulmonary infection. Within a few days of the onset of the pneumonia there is usually a polymorphonuclear leucocytosis, the total white blood count being of the order of 15,000 to 20,000 cells per c.mm. The leucopenia seen in fulminating cases is seldom encountered.

6. *Sequelae.* In these cases of modified virulence complete recovery is to be expected. A few patients retain a cough and dyspnoea caused by bronchiectasis, by emphysema, or by a chronic lung abscess or empyema. A few, though symptomless, show in their chest skiagram one or more large air-containing spaces. Of Brock's (1945) 24 patients who survived there was evidence of permanent lung damage in 12; this, as he remarked, is not surprising when one sees the severe and extensive damage done to the lung during the acute phase of the illness. The introduction of penicillin has greatly lessened the ultimate morbidity. Of our 10 patients only one was left with a residual pulmonary lesion for which the staphylococcal pneumonia could be incriminated. Similarly satisfactory results were reported by Bennett and Parkes (1944) and by Davis, Hyman, and Ruhstaller (1947).

Case Reports

The following 10 cases of acute but non-fulminating staphylococcal pneumonia occurred during the 1949 influenza epidemic between January and March. They were seen in seven quite unrelated London hospitals.

Case 1. Mrs. C. B., age 51 years, developed a right-sided pleural pain six days from the onset of typical influenza. She did not improve with sulphonamide therapy at home, but was in fairly good condition when admitted to hospital 10 days later. She was found to have a localized right basal pyopneumothorax, with patchy consolidation throughout the right lung. There was a leucocytosis of 18,600 (75 per cent. polymorphs) per c.mm. *Staphylococcus aureus* was obtained in pure culture from the empyema pus and from the sputum. She improved rapidly on a régime of penicillin, given intramuscularly and intrapleurally, with repeated aspiration of empyema pus. She was free of symptoms when discharged after six weeks in hospital, and the lung was radiologically clear 14 weeks from the onset of her pneumonia.

Case 2. R. E., aged 27 years, was acutely ill when admitted to hospital 14 days after the start of influenza. He was dyspnoeic and blue, and complained of

right basal pleural pain. He had the signs of right middle and lower lobe pneumonia (Plate 14, Fig. 7), and his white blood-cells were 13,400 per c.mm. (85 per cent. polymorphs). An almost pure growth of *Staphylococcus aureus* was obtained from his sputum. His response to systemic penicillin was dramatic, and radiological resolution was virtually complete three weeks from the start of the pneumonia.

Case 3. W. J., aged 61 years, a chronic bronchitic, while in hospital owing to carcinoma of the bladder, developed a cough, malaise, and left-sided pleurisy. Five days later there were signs of pulmonary consolidation, and chest X-rays revealed an enormous abscess in the left upper lobe, with some patchy opacities at the left base. The sputum yielded a profuse growth of *Staphylococcus aureus*. Though he was at no time seriously ill, there was rapid clinical improvement on medical treatment. The initial treatment with penicillin was changed to streptomycin and sulphamerazine owing to a sensitization rash. Radiologically, progress was slow, but three months from the onset the only remaining abnormality was slight residual fibrosis at the site of the original abscess.

Case 4. J. W., aged 60 years, gave a history of six weeks' malaise, fever, and cough. On admission he was orthopnoeic, with cyanosis, and was producing quantities of purulent pinkish sputum from which *Staphylococcus aureus* was grown in almost pure culture. There was clinical and radiological evidence of left upper lobe consolidation, and his white blood-cells were 22,000 per c.mm. (78 per cent. polymorphs). He was treated with sulphamerazine and penicillin. For the first four days he remained very ill, but thereafter slowly improved. It was not until four weeks after admission that the dense left upper lobe opacity had sufficiently cleared to reveal multiple abscess cavities. These very gradually disappeared, and a normal X-ray was obtained four months from the time of admission.

Case 5. Miss I. L., aged 30 years, was admitted in an acute attack of asthma, a disease to which she had been subject since childhood. Her bronchospasm was quickly relieved by adrenalin, but she remained very ill, with a high fever and productive cough. A heavy growth of *Staphylococcus aureus* was obtained from her sputum. An X-ray on admission showed a little mottling at both apices. In spite of adequate systemic penicillin, with which she made good clinical progress, serial skiagrams showed that the disease developed along its usual course to consolidation and multiple cavity formation and then gradually abated, taking in all seven months for resolution to be radiologically complete (Plates 11, 12, 13, Figs. 1 to 5).

Case 6. Mrs. V. W., aged 40 years, while in hospital for a skin-grafting operation, developed an influenza-like illness in which there was at first no clinical or radiological evidence of pulmonary involvement. Her condition deteriorated until seven days later, when she complained of right pleural pain. A friction was heard, and an X-ray showed considerable infiltration in the right upper and left lower zones. From her sputum *Staphylococcus aureus* was grown in pure culture. She was treated with penicillin and later, owing to a poor initial response, received streptomycin in addition. At no time was there cavitation, but it took several months for resolution to be complete.

Case 7. F. H., aged 14 years, was admitted to hospital 14 days after the onset of influenza. He was dyspnoeic, and distressed by right-sided pleural pain. Physical signs of right lower lobe consolidation were detected, and an X-ray revealed two large abscess cavities in this region of the lung (Plate 15, Figs. 8

and 9). From his rusty sputum a profuse growth of *Staphylococcus aureus* was obtained. His white blood-cells were 14,300 per c.mm. (73 per cent. polymorphs). He quickly improved with penicillin, sulphatriad, and postural drainage, and a normal right bronchogram was obtained nine weeks from the date of his admission.

Case 8. W. J. W., aged 74 years, became ill with what appeared to be a febrile exacerbation of his chronic bronchitis. His appearance on admission 10 days later was that of an acutely ill old man with severe right-sided pleuritic pain. He was cyanotic and dyspnoeic, and had herpes labialis. There was clinical and radiological evidence of right lower lobe pneumonia. A culture of his blood-stained sputum yielded *Staphylococcus aureus* as the predominant organism. His white blood-cells were 17,500 per c.mm. (84 per cent. polymorphs). He reacted slowly but favourably to penicillin and sulphadiazine, and the chest X-rays, which at no time showed cavitation, were almost clear seven weeks from the start of his illness.

Case 9. Mrs. E. M. B., aged 42 years, complained of a gradual onset during the previous month of malaise, productive cough, and substernal pain. On admission she was a pale, ill-looking woman, and was found to have extensive consolidation of the left mid-zone, with central cavitation. Tubercle bacilli were not seen in seven specimens of her copious blood-stained sputum, but on culture *Staphylococcus aureus* and *Staphylococcus albus* were grown. She improved with penicillin and sulphatriad combined with postural drainage, and an X-ray taken four weeks from her admission showed considerable clearing of the pneumonia and disappearance of the cavity. Thereafter her condition deteriorated, and fresh infiltration appeared in the right lung. This infiltration was not reduced by a further course of penicillin, and her sputum contained numerous tubercle bacilli. There seems to be little doubt that the pneumonia lit up a dormant tuberculous focus.

Case 10. Mrs. M. W., aged 30 years, was admitted 12 days after the onset of an attack of influenza which had persisted. Her cough had become productive of a brownish pink sputum. She appeared ill, and had the physical and radiological signs of left upper lobe consolidation. An X-ray showed two large abscess cavities in this area. She had a leucocytosis of 15,600 cells per c.mm. (87 per cent. polymorphs) and culture of the sputum yielded *Staphylococcus aureus*. She was free of symptoms and her lungs were clinically normal five weeks from the date of her admission, for her condition quickly improved with penicillin. For several months, however, two small thin-walled empty cavities were visible radiologically.

Radiological Features

At the onset of the pneumonia the chest film reveals diffuse mottling of a 'bronchopneumonic' rather than a miliary quality. This may be scattered throughout both lungs or localized to one or more lobes (Plate 11, Fig. 1). Serial films show a rapid change during the course of a few days. The initial opacities appear to coalesce until there is massive consolidation of a lobe or lobes. At this stage the majority of patients with fulminating pneumonia die of profound toxaemia, whereas the mild cases proceed to resolve, following the radiological course of a typical bacterial pneumonia. In patients with the acute but non-fulminating disease who survive, multiple cavity formation will now appear, giving the radiological picture characteristic of the disease

(Plate 11, Fig. 2). One or more of these cavities may become extremely large. They may show a distinct fluid-level or may be completely empty, according to their relationship to the communicating bronchus (Plate 15, Figs. 8, 9). Bronchogenic spread of infection is not infrequent, leading to fresh areas of mottling in lung which before was radiologically normal. This extension seldom proceeds to cavity formation, and rapidly clears if the patient is receiving adequate treatment. Though multiple cavitation is more usual, sometimes a single large abscess is seen. As the massive consolidation gradually resolves, the cavities may become more clearly defined (Plate 12, Fig. 3). The facts that they are spherical or ovoid, that their walls appear radiologically to be thin and smooth, that they frequently contain little or no fluid, that they persist when the surrounding consolidation has largely resolved, and that in most cases they finally disappear leaving a normal lung, suggest that they are due more to distension than to lung destruction. As is thought to be the case in the production of tuberculous cavities, the mucous membrane of a bronchus leading to a diseased area of lung becomes oedematous and acts as a one-way valve. On inspiration the bronchus dilates and allows air to pass, but during the subsequent phase of expiration and bronchial contraction air cannot be expelled until the pressure within the cavity rises sufficiently to render the one-way valve no longer mechanically competent. This check-valve mechanism appears also to play a major part in the production of the tension pyopneumothorax—a frequent complication among children. The child's lung is presumably more fragile than that of an adult, and therefore more liable to rupture when subjected to positive pressure. A pyopneumothorax is difficult to diagnose radiologically unless the X-ray is taken with the patient in the upright position (Plate 14, Fig. 6). Residual cavities in the lung, variously described as of 'egg-shell' or 'soap-bubble' appearance, may remain for many weeks after the acute phase of the illness has passed and after resolution of the surrounding consolidation is radiologically complete (Plate 12, Fig. 4). In the majority of patients these cavities will eventually disappear, leaving a clear lung or a small linear scar—a process which in our series took on the average four months. In a few patients they will persist indefinitely, and in later years they may easily be mistaken for congenital cysts of the lung.

Pathology

At first the affected areas of lung are intensely hyperaemic. Microscopically the picture is one of haemorrhage and oedema, with necrosis of alveolar walls and the presence of numerous groups of staphylococci. The next stage is characterized by the appearance of miliary abscesses. These rapidly increase in size, and are seen to be lying in close relation to the bronchioles, into which they soon discharge their contents and with which they remain in communication. The check-valve mechanism caused by oedematous obstruction of the bronchus now comes into play, and one or more of the cavities may be blown up to relatively enormous dimensions. Many of them are subpleural, and may rupture into the pleural cavity and produce empyema or pyopneumothorax. Infants in

particular may succumb before large abscess cavities are formed, probably because of the high incidence of tension pyopneumothorax in this age-group. Resolution takes place gradually, with liquefaction and absorption of the exudate. Residual cavities may remain for many months after the inflammatory process of the surrounding lung has resolved, but the majority shrink and close during the first eight weeks of the illness. In a small percentage of cases residual bronchiectasis, emphysema, or large dry air-containing spaces remain.

A bacteriological criterion in the diagnosis of this disease is the growth of the staphylococcus in pure or almost pure culture from the sputum, lung puncture, or empyema fluid. In many cases of pneumonia a culture from these sources will yield a mixed flora, of which the staphylococcus is one of the many organisms present. Experience has shown that, unless the staphylococcus is at least the predominant organism, such cases are not staphylococcal pneumonias as judged by their clinical and radiological course. The *Staphylococcus albus*, usually dismissed as a harmless skin saprophyte, can on rare occasions become pathogenic. In five of the 40 cases of primary staphylococcal pneumonia described by Blumenthal and Neuhof (1946) it was proved to have been the offending organism. The relationship of staphylococcal pneumonia to influenza is of singular interest. From 1896 onwards the various writers who have reported influenza epidemics have been struck by the apparent synergism between the staphylococcus and the influenza virus. McCordock and Muckenfuss (1933) were able to produce in rabbits a lobular pneumonia with multiple abscess formation by the intratracheal injection of a combination of *Staphylococcus aureus* and a virus. Many of these rabbits died, and those which had received a large dose of *Staphylococcus aureus* died within 48 hours. The virus alone in small quantities gave rise to a non-fatal proliferative 'interstitial' pneumonia, but in higher concentration caused an acute necrotizing tracheobronchitis with a haemorrhagic consolidation of bronchopneumonic distribution. In describing the focal suppurative lesions produced by the combined administration of staphylococci and virus, they observed, 'Microscopically some of these irregular abscesses appear to have been produced by the bacteria spreading rapidly from the central bronchiole throughout an area that had already been rendered necrotic by the action of the virus'. Scadding (1937), in reporting an influenza epidemic, observed that in all the fatal cases tracheal and bronchial inflammation with epithelial desquamation was prominent, amounting at times to a necrotizing process, which was well demonstrated in the one patient who died of fulminating staphylococcal pneumonia. He concluded that 'a pure influenza-virus infection of the human lung can probably descend to any level of the respiratory tract. If it proceeds to an actual alveolitis, a clinical picture of oedematous lung bases with possibly some actual patchy consolidation is produced. Such virus pneumonias are very rarely, if ever, fatal before invasion of the lung by bacteria, usually pneumococci, haemolytic streptococci, Pfeiffer's bacilli or staphylococci, has occurred.' From observation of our own cases and from a critical study of those reported in the literature, we feel that it is highly probable that all cases

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of 'primary' staphylococcal pneumonia are preceded by a mild virus infection of the respiratory tract.

Treatment

1. *Medical.* Writing of their considerable experience in the 1918–19 epidemic, Chickering and Park said: 'The treatment of *Staphylococcus aureus* infections of the lung is singularly ineffectual.' This grave pronouncement was true until the advent of the sulphonamides. Finland, Peterson, and Strauss (1942) reported considerable benefit in their 60 patients who received this form of chemotherapy. Twenty-one died out of a series of 66 patients, but seven of the 21 had fulminating pneumonia. Four of the six who had empyemata recovered completely with sulphonamide therapy and repeated aspiration. In addition there were six patients who developed sterile pleural effusions, and this fact was interpreted as further indication of the efficacy of chemotherapy. There is nothing to choose in effect between sulphadiazine and sulphathiazol. The usual dose given is one gramme every four hours until the temperature has been normal for two or three days. Some writers have been disappointed in the sulphonamides, feeling that they influenced the course of the pneumonia little if at all (Blumenthal and Neuhof, 1946; Davis, 1944). Most workers have been impressed with the striking results of penicillin therapy in this disease (Blake and Craige, 1942–3; Bennett and Parkes, 1944; Blumenthal and Neuhof, 1946; Dickey, 1950). Our own experience with penicillin has been entirely satisfactory. All our patients received both penicillin and sulphonamides. We feel that a combination is preferable to penicillin given alone, and base this opinion upon the suggestion of a synergistic action between the two drugs (Bigger, 1944). The report of the 1949 influenza epidemic in Sheffield by Stuart-Harris, Franks, and Tyrrell (1950), shows that penicillin is not the final answer to the problem, for of 22 fatal cases investigated in hospital, the cause of death in 10 was staphylococcal pneumonia, and all these patients had been adequately treated with penicillin and sulphonamides. There is little agreement as to the optimum dosage of penicillin. Quantities varying from 20,000 to 200,000 units have been given at three-hourly intervals. Two of our patients responded rapidly to 300,000 units of a preparation of procain-penicillin by a single daily intramuscular injection, and we feel that this dosage will suffice in most cases. The duration of treatment should be dictated by the clinical rather than the radiological progress. Once the patient has had no pyrexia for three or four days it is generally safe to stop both penicillin and sulphonamide. Although at this stage infiltration and cavitation are still very evident radiologically, experience has shown that resolution will proceed slowly, aided by postural therapy and breathing exercises, and that it will not be hastened by the continuation of chemotherapy. There is good reason to believe that the newer antibiotics will be of even greater service in the treatment of primary staphylococcal pneumonia. Schwachman, Crocker, Foley, and Patterson (1949) published dramatic results with aureomycin given by mouth. The outcome of this treatment was 'excellent to good' in 31 of their 35 cases of fibrocystic disease of the pancreas in which pulmonary infection was

due to the *Staphylococcus aureus*. They emphasized the prompt return of symptoms when the drug was discontinued, a sequel which was only to be expected in view of the irreversibility of the pulmonary changes.

2. *Surgical.* The problems of surgical treatment are the management firstly of collections of pus, or pus and air, in the pleural cavity, and secondly of any localized lung abscess that may arise. An empyema if left to absorb on its own will result at best in massive pleural thickening, with gross diminution of the functional capacity of the underlying lung. All writers are agreed that such collections of pus should be removed. Most of those who advocated closed, or even open, drainage of the pleural cavity were writing in the years before they had experienced the striking effects of penicillin (Blumenthal and Neuhof, 1946; Brock, 1945). Though the more active measures may still be necessary in a very few cases, it now appears that the great majority of staphylococcal empyemata and pyopneumothoraces will resolve with daily aspiration and the instillation of 30,000 to 50,000 units of penicillin, leaving no more pleural thickening than that which results from continuous drainage with or without rib resection. This inference is borne out by our limited experience, and by the work of Davis, Hyman, and Ruhstaller (1947). They observed that, though the empyema pus becomes sterile on culture within a few days, staphylococci are still visible in the direct films for some time longer. Intrapleural penicillin should be continued until the smears are free of the organism. In the treatment of intrapulmonary suppuration the weight of opinion is heavily against surgical interference. Brock (1945), writing of patients treated by him even prior to the penicillin era, said: 'I believe that almost all staphylococcal lung abscesses should be treated conservatively—the fundamental therapeutic approach should be non-surgical. . . . However ill the patient has been and however large or extensive the abscesses, I have recommended continuance of chemotherapy and postural drainage alone, and in 18 consecutive cases this policy has been followed by the complete recovery of the patient.' We entirely agree with this opinion, and are convinced that it was right not to subject any of our 10 patients to external drainage. The rare examples in which a chronic lung abscess persists should be treated by resection of the affected lobe or bronchopulmonary segment.

Acknowledgements

We are indebted to Dr. H. L. Marriott, to Professor E. P. Sharpey-Schafer, and to the Medical Superintendents of the Archway Hospital Group, of St. Mary Abbots Hospital, of the Paddington Hospital, and of St. Stephen's Hospital, Fulham, for giving us access to their patients. The present article is based on a paper read by one of us (J. R. B.) to the Thoracic Society.

Summary

1. Primary staphylococcal pneumonia must be distinguished from staphylococcal infection of the lungs which may occur during the course of a septicaemia arising from a distant focus.

2. The primary form of the disease may arise sporadically, this variety being almost confined to infants and young children, and being frequently complicated by empyema or tension pyopneumothorax. These complications may account for the high mortality of the disease in these patients.

3. Alternatively the disease may be preceded by a virus infection, influenza being by far the most common precursor of staphylococcal pneumonia. This type of the disease most frequently affects adults, some of whom have pre-existing pulmonary lesions. In the past it has often been fulminating and rapidly fatal; more recently, apart from the influence of chemotherapy, the disease appears to have taken a milder form. The histories of 10 patients in this latter group are described in detail.

4. The radiological course of staphylococcal pneumonia may be described as having three phases: the phase of pneumonia, the phase of abscess formation, and the phase of cyst formation. The second and third are the most characteristic, and the cyst which may be formed as a sequel to staphylococcal pneumonia may be present for many months without causing any symptoms.

5. Modern antibiotic therapy has entirely altered the prognosis of this disease, and in the present series no death occurred. The authors conclude that all patients should receive adequate, but not necessarily enormous, doses of penicillin and sulphonamides; that drainage of the abscess cavity should not be considered, but that resection may be necessary at a later stage in a few patients; and that the duration of chemotherapy should be governed by the clinical condition of the patient, and not by the appearance of the radiographs.

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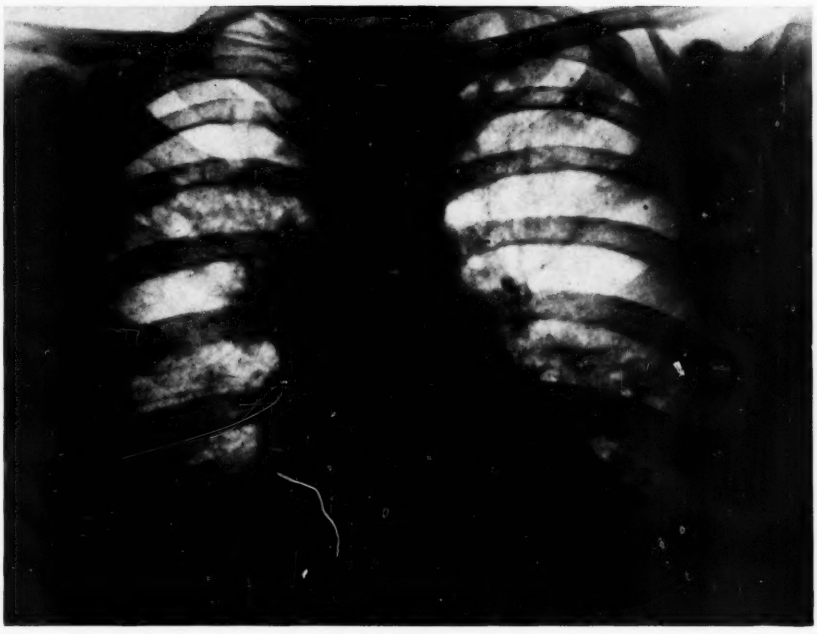


FIG. 1. Case 5. Patchy consolidation in right and left upper and middle zones

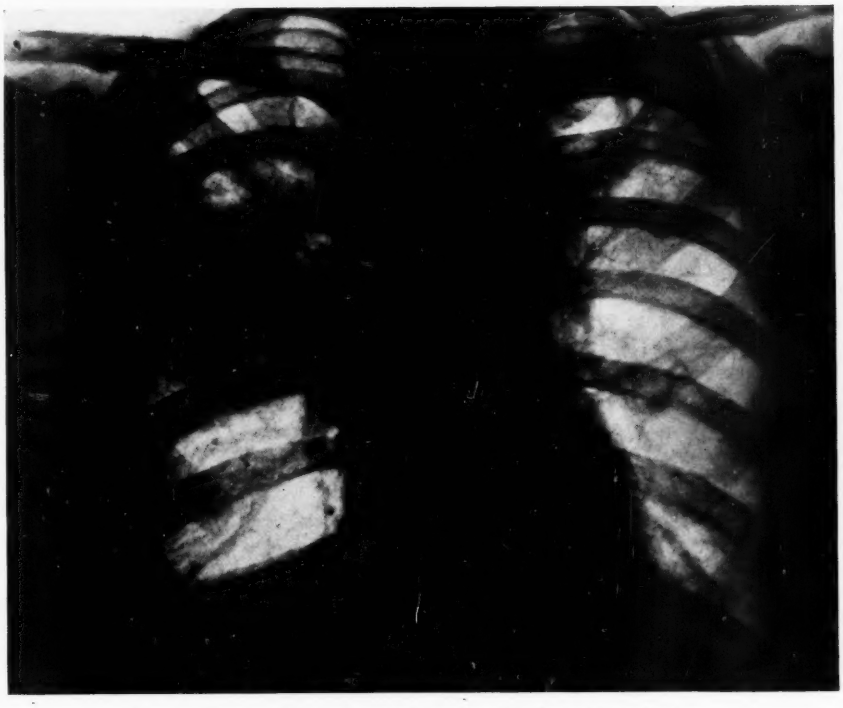


FIG. 2. Case 5. Bilateral upper lobe consolidation with cavitation

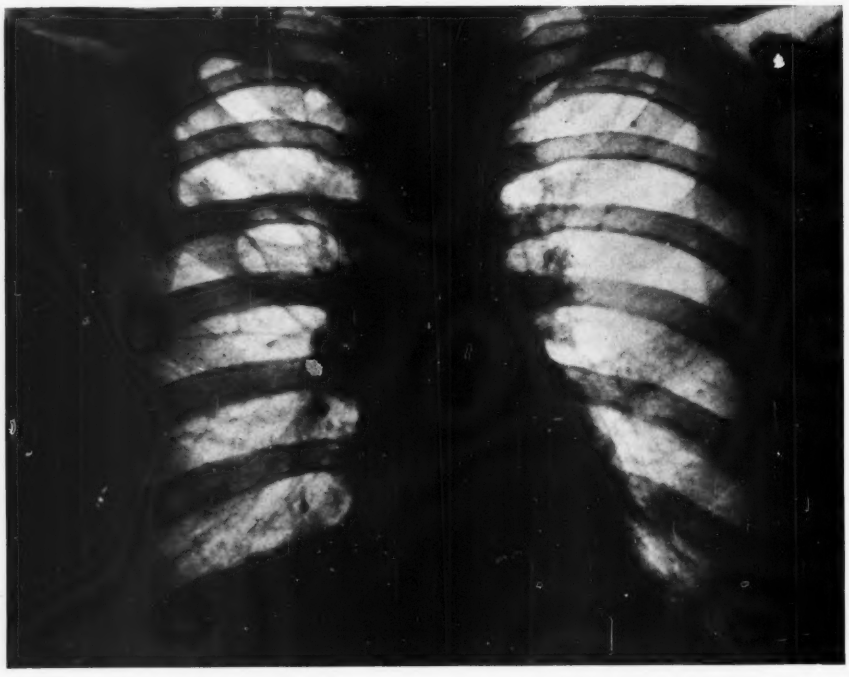


FIG. 3. Case 5. Consolidation almost resolved; a large cavity remains in the right upper lobe

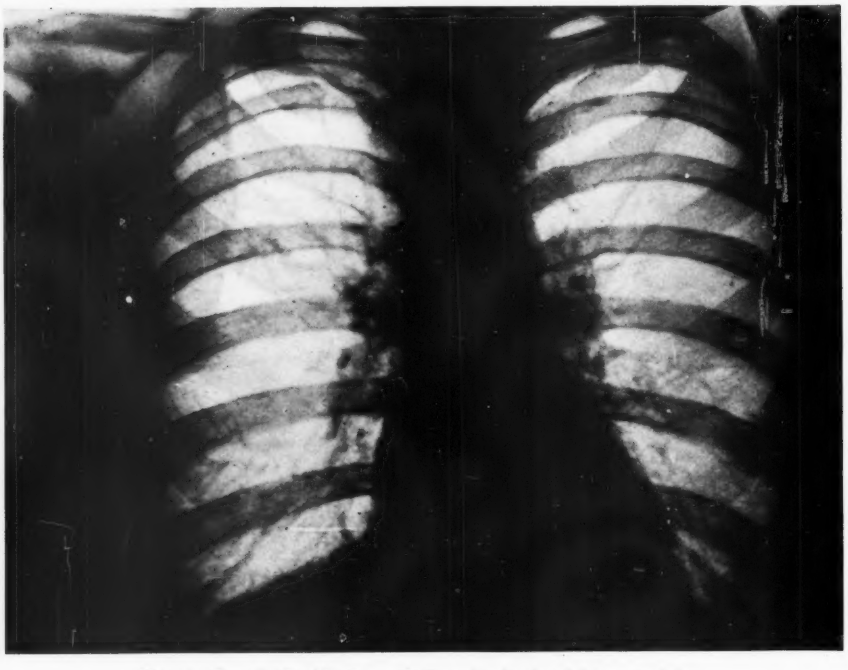


FIG. 4. Case 5. Residual egg-shell cavity in the right upper lobe

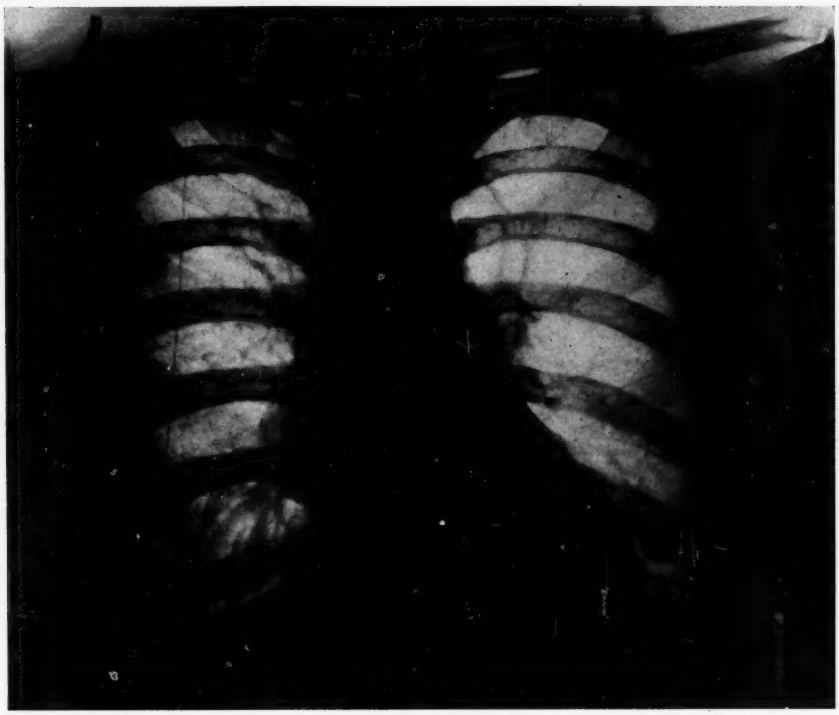
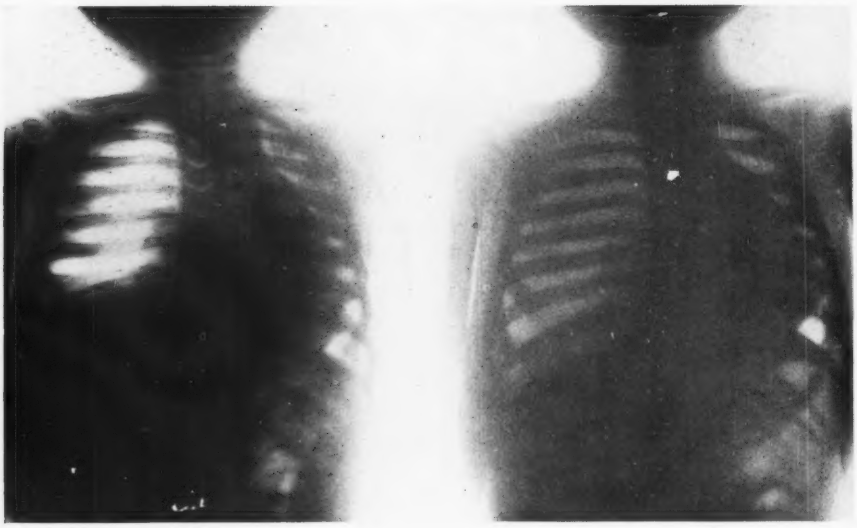


FIG. 5. Case 5. Resolution complete



a *b*

FIG. 6. Pyopneumothorax: patient (*a*) upright and (*b*) lying down

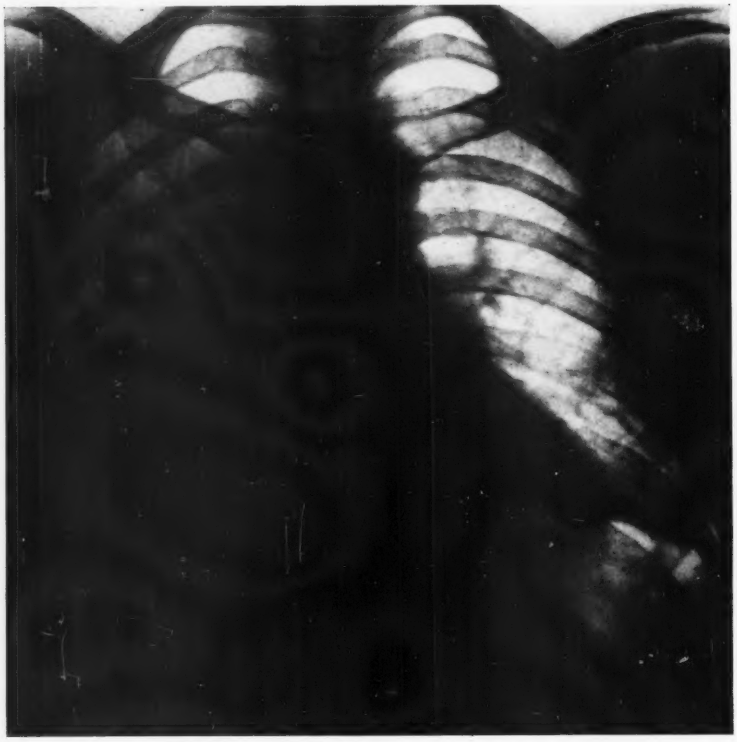


FIG. 7. Case 2. Right middle and lower lobe consolidation

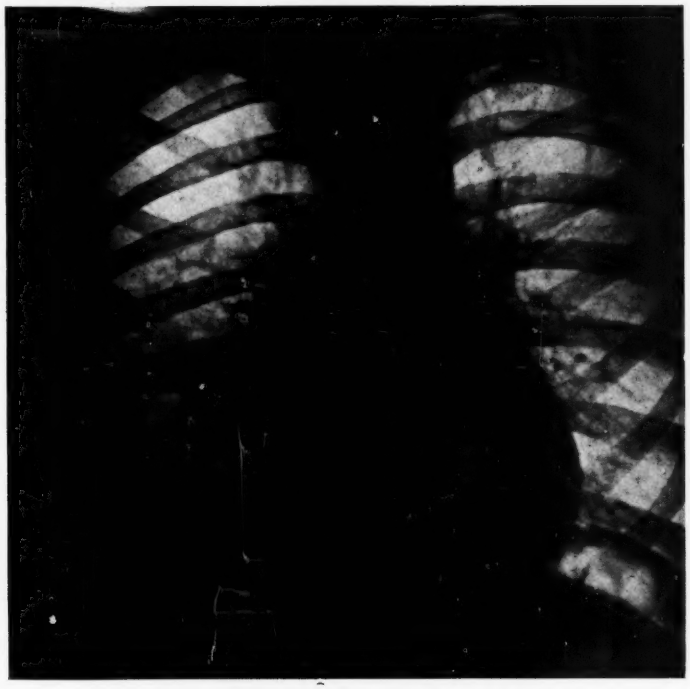


FIG. 8. Case 7. Large abscess cavities in right lower lobe

FIG. 9. Case 7. Large abscess cavities in right lower lobe; lateral view

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FELTY'S SYNDROME

A REPORT OF FOUR CASES TREATED BY SPLENECTOMY[1]

By M. S. R. HUTT, J. S. RICHARDSON, and J. S. STAFFURTH

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Involvement of the reticulo-endothelial system in rheumatoid arthritis was first recorded by Chauffard and Ramond (1896) when they noted the presence of lymphadenopathy in seven cases. In the following year Still (1897) described 12 children with arthritis who had enlarged spleens as well as lymphadenopathy, but none showed alteration in the blood picture. McCrae (1904), in a discussion on rheumatoid arthritis, reported the case of a young man with the signs described by Still. He considered these to be a peculiar response dependent on the age of the patient, and not the signs of a separate disease. Between McCrae's report and that of Felty (1924) isolated cases of rheumatoid arthritis were recorded with both lymphadenopathy and splenomegaly (von Jaksch, 1908; Herringham, 1909; Pollitzer, 1914; Schmidt, 1917). An exhaustive review of the literature by Singer and Levy (1936) revealed the frequency with which this association of signs had been noted, though none of the authors before Felty had grouped the features as a syndrome. Felty (1924) described five cases occurring in middle-aged men and women, who presented the signs of a gradually progressive arthritis of the rheumatoid type, splenic enlargement, and, as an essential feature, an abnormal blood picture with neutropenia. In three cases lymphadenopathy was noted, and all had some degree of pigmentation of the exposed skin-surfaces. The blood picture in four patients showed a mild hypochromic anaemia, while in every case there was a leucopenia. The figures ranged from 1,000 to 4,200 white cells per c.mm. Felty considered that this association of findings must be due either to a single pathological process or to two separate processes occurring as a coincidence in the same individual. He thought the latter suggestion the less probable, and went on to state, 'One is more or less forced to the conclusion that this syndrome is a clinical entity of which the outstanding symptoms are those related to the joints, and the outstanding signs are the enlarged spleen and the blood picture'. Since 1924 numerous reports of the syndrome have appeared in American and Scandinavian literature (Hanrahan and Miller, 1932; Craven, 1934; Fitz, 1935; Williams, 1936; Singer and Levy, 1936; Curtis and Pollard, 1940; Edstrom, 1941; Steinberg, 1942; Gyntelberg, 1942; Talkov, Bauer, and Short, 1942; Trolle and Trolle, 1943; Eikelund, 1943; Zimmer, 1945; Hatch, 1945; Hirschboeck, 1946; Ytrehus, 1946–7; Smith and McCabe, 1948; Peden, 1949), but although the condition is not uncommon, few direct references to it are to be found in the

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British literature (Gauld, 1949). We propose in the present paper to describe four patients with Felty's syndrome in whom splenectomy was carried out, and to discuss the clinical and therapeutic problems that they presented.

Case Histories

Case 1. N. C., a man aged 60 years, was admitted to hospital at the end of 1948. He began to get rheumatic pains in 1940, and these pains troubled him on and off until late in 1945, when they became more severe and limited his activity to an increasing extent. During the year before admission he had felt generally ill, with dyspnoea on exertion and increasing pain from his joints, and in the last six weeks he had had severe abdominal pain due to perisplenitis. In 1936 a laparotomy had been performed. The reason for this operation is not clear, but he was told that there was an inflammatory mass which was neither malignant nor tuberculous. He served in the army from 1939 to 1941, when he was discharged because of abdominal symptoms related to the laparotomy. On examination he was a thin, ill man in obvious abdominal pain. He was unable to shake hands owing to flexion deformity of both elbows and to the complete crippling of his hands. The hands showed gross changes of 'burnt-out' rheumatoid arthritis, with ulnar deviation, very lax ligaments, and flail fingers. The elbows were flexed, and extension was limited to 150 degrees; the knees were held in flexion, and could not be extended beyond 120 degrees. The hips and ankles were relatively unaffected. The spleen was palpable four inches below the costal margin, and over it a harsh friction could be heard. The liver was just palpable below the costal margin. There was enlargement of the right epitrochlear and left axillary lymph glands. No abnormality was found in the heart and lungs. The blood-pressure was 130/80, and the urine contained no abnormal constituents. Blood counts showed an anaemia and leucopenia (Table I). The erythrocyte sedimentation rate was 66 mm. in one hour; the Wassermann reaction was negative, the thymol turbidity 8 units, serum alkaline phosphatase 10·2 units, icteric index 3 units, and plasma-proteins 7·0 gm. per 100 ml. (albumin 3·2 gm., globulin 3·8 gm.). Sternal marrow biopsy showed polymorphonuclear cells 18 per cent., lymphocytes 5·5 per cent., eosinophils 0·5 per cent., metamyelocytes 6·0 per cent., neutrophil myelocytes 33·5 per cent., promyelocytes 1·5 per cent., myeloblasts 2·5 per cent., and normoblasts A 7·0 per cent., B 5·0 per cent., C 20·5 per cent. X-rays showed changes associated with advanced rheumatoid arthritis.

An operation was performed on February 1, 1949, when a large, friable spleen was removed which had recent adhesions to the diaphragm. The liver looked normal, but no biopsy was done. The spleen weighed 1,390 gm., and on section showed the normal general architecture. Microscopically there was a fair number of normal-sized lymphoid follicles, and the fibrous tissue septa were not increased. The sinuses were abundant, and there appeared to be proliferation of the endothelial cells. Reticulin-stained sections showed a normal pattern. No phagocytosis of cells was seen. Progress after the operation was remarkable. Within 24 hours he said that his hands began to feel less stiff, and 48 hours later it was possible for him to extend his elbows to 170 degrees—a thing he had not been able to do for four years. His general health improved steadily, and on his discharge three weeks later he was able to stand reasonably straight, could walk across the room, and could stand on one leg while putting on his slipper. The knees and hips had almost full movement, but there was no change in the hands. Blood counts after operation showed immediate return of the white blood-cells to normal levels; the improvement in the anaemia (Table I) was

largely due to blood transfusion. In March 1950, over a year after the operation, he reported that his joints were freely mobile except for the hands, which were stiff and feeble but were still getting stronger. He was able to walk a mile without tiring, and was working five hours a day on a hand-loom. He regarded

TABLE I

	Date	Haemoglobin (%)	Red blood-cells (millions per c.mm.)	White blood-cells: per c.mm.	polymorphs %	eosinophils %	basophils %	lymphocytes %	monocytes %	Platelets (per c.mm.)
Pre-operative	18. 3.46	76	4·24	7,480	71	..	2	23	4	..
	18.11.48	42	3·08	1,200	47	2	1	45	5	470,000
	31. 1.49	50	3.17	2,800	21	..	..	79	..	..
Operation	1. 2.49	..	..	..	..	..	..	..	..	..
Post-operative	2. 2.49	80	4·53	6,900	77	..	..	23	..	298,000
	22. 2.49	91	4·82	6,000	69	..	..	31	..	..
	22. 9.49	96	4·75	7,400	39	4	..	54	3	..

his general health as good, and was very pleased that he had undergone the operation. The improvement in the anaemia and leucopenia was maintained.

Summary. A man aged 60 years was severely incapacitated by rheumatoid arthritis, which had first appeared eight years earlier. He was found to have splenomegaly, anaemia, and leucopenia. After splenectomy there was striking improvement in his joint symptoms, and the blood count became normal. This improvement was maintained one year later.

Case 2. D. R., a married woman aged 46 years, was admitted to hospital on January 1, 1949. She had had no other serious ailments. She had one child aged 14 years. Her periods had been irregular since 1942, and ceased in 1948. Symptoms of rheumatoid arthritis were first noticed in 1942 with pain and swelling in the hands, and later most of the other joints were involved. She spent four months in hospital in 1943, and at that time had leucopenia; 11 of 13 blood counts showed between 1,800 and 3,600 white cells per c.mm., with absolute neutropenia. There was a relapse of the arthritis in 1946, when three further blood counts showed 3,200 white cells per c.mm. The arthritis became quiescent, and she remained reasonably well until August 1948, when an ulcer developed on the left foot after treatment by a chiropodist. This ulcer persisted and led to her admission to hospital in January 1949, after which it healed in three weeks. She then began to get severe ulceration in the mouth, which for three months resisted all forms of treatment. Bilateral conjunctivitis appeared at the same time, and was later complicated by a corneal ulcer in the right eye. On examination her general condition was poor. Ulceration about the mucocutaneous junction of her mouth was very severe, and there were less severe ulcers inside the mouth. There was bilateral conjunctivitis, and a corneal ulcer in the right eye. The hands showed the gross deformity of long-standing 'burnt-out' rheumatoid arthritis. The right wrist was fixed and movement at the left wrist was poor, but the elbows, shoulders, knee- and ankle-joints all had full movement. The right hip had 30 degrees of fixed flexion, but such movement as there was was painless. The left hip showed some limitation of movement in all directions. The toes had deformities similar to those in the hands. Lymph

glands were felt in the supraclavicular fossae, the anterior triangle of the neck, the left axilla, the left epitrochlear region, and both inguinal regions. The spleen was palpable five inches below the costal margin, and the liver was just palpable. No abnormality was found in the heart and lungs. The blood-pressure was 120/60, and the urine contained no abnormal constituents. Blood counts showed anaemia and leucopenia (Table II). The erythrocyte sedimentation rate was 86 mm. in one hour; the Wassermann reaction was negative, thymol

TABLE II

	Date	Haemoglobin %	Red blood-cells (millions per c.mm.)	White blood-cells: per c.mm.	polymorphs %	eosinophils %	basophils %	lymphocytes %	monocytes %	Platelets (per c.mm.)
Pre-operative	20.7.43	..	..	2,400	21	4	6	61	8	..
	3.1.46	..	..	3,200	62	2	5	24	7	..
	5.1.49	51	2·95	3,900	56	..	..	43	1	..
	18.3.49	50	2·62	750	20	..	..	80	..	93,000
Operation	23.3.49	..	..	..	..	..	..	..	..	..
Post-operative	25.3.49	68	3·27	7,100	68	..	..	32	..	139,000
	22.4.49	78	3·94	4,900	72	..	..	27	1	..
	9.2.50	90	4·80	8,000	54	..	..	46	..	..

turbidity 22 units, serum alkaline phosphatase 7 units, and plasma-proteins 8·2 gm. per 100 ml. (albumin 3·1 gm., globulin 5·1 gm.). Sternal marrow biopsy showed polymorphonuclear cells 23·5 per cent., lymphocytes 3·0 per cent., eosinophils 2·0 per cent., neutrophil myelocytes 48·0 per cent., eosinophil myelocytes 1·0 per cent., myeloblasts 0·5 per cent., and normoblasts B 1·0 per cent., C 21·0 per cent. X-rays showed the changes associated with advanced rheumatoid arthritis.

Splenectomy was performed on March 23, 1949. The spleen weighed 1,258 gm., and on section showed fairly prominent Malpighian bodies. Microscopically there was increased cellularity, caused partly by an increase of blood-cells, but largely by an increase of sinus endothelial cells. A small amount of blood pigment was present, but there was no increase of fibrous tissue. The liver showed slight lymphocytic infiltration in the portal tracts, but there was no evidence of fibrosis. Post-operative progress was striking. Within three days her mouth and eyes cleared completely, and she was able to eat without discomfort. Her colour and general condition rapidly improved, but she complained of pains in her arms. On April 12, 1949, the arthritis flared up, affecting both ankles, both knees, both hips, and both shoulders. This did not prevent her discharge from hospital on April 23, when her general condition was greatly improved, with an increase in weight and appetite. Two days after operation the white blood-cells were 7,100 per c.mm., and since then have remained at low normal figures (Table II). When she was seen in May and June 1949, the general improvement was maintained, but she continued to have pain and swelling in the knees, hands, and shoulders. In February 1950 she felt better than she had done for years. The arthritis had settled down, and she felt better than during a quiescent phase before operation. The ulcer of the foot remained healed, and she had had no further trouble with the mouth or eyes. She was perfectly clear in her own mind that the operation had benefited her to a considerable degree. The blood count was normal (Table II).

Summary. A married woman, aged 46 years, had had rheumatoid arthritis for seven years. A chronic ulcer developed on the left foot after treatment by a chiropodist. This healed after admission, but she then got painful ulcers in the mouth and bilateral conjunctivitis, with a corneal ulcer in the right eye. She was found to have splenomegaly, anaemia, and leucopenia. Splenectomy was performed three months later, and resulted in a dramatic cure of the mouth and eyes. Two weeks after operation there was a relapse of the arthritis, but it slowly improved, and was quiescent one year later; there had then been no recurrence of the ulcer, and the blood count remained normal.

Case 3. M. A., a single woman aged 52 years, was admitted to hospital on December 30, 1948. Symptoms of rheumatoid arthritis had first been noticed in 1920, when she was admitted to hospital with generalized pain and stiffness of the joints. During the next 25 years the arthritis had steadily deteriorated, and in 1946 she was admitted to a home for incurables as a complete cripple. We know that in 1935 the spleen was not palpable, and that her white cells were then 6,800 per c.mm. There had been no other serious illnesses, and the menopause occurred at the age of 48. One week before admission she had developed a hypopyon ulcer in the right eye which failed to respond to local treatment, and the eye had to be excised for panophthalmitis. Episcleritis developed in the left eye on January 26, 1949, and limbal corneal ulcers soon followed. These ulcers slowly advanced until only the upper quarter of the cornea was unaffected. She had noticed recurrent painful ulcers in the mouth since the eye complaints began. The shoulder-joints were a little painful, but the arthritis was otherwise quiescent. On examination in March 1949 she had no pyrexia and was in fair general condition. There were three shallow, painful ulcers on the inside of the mouth. The hands showed gross deformity due to 'burnt-out' rheumatoid arthritis. Full flexion was possible at the elbows, but extension was limited. Movement of the shoulder-joints was limited by pain. She was unable to sit up owing to fixed deformity of the hips, and there was firm ankylosis of the knees. The feet and ankles were also severely affected. The spleen was palpable three inches below the costal margin, and the liver could just be felt. There was no lymphadenopathy. No abnormality was found in the heart or lungs. The blood-pressure was 150/90, and the urine contained no abnormal constituents. Blood counts showed slight anaemia and leucopenia (Table III). The erythrocyte sedimentation rate was 35 mm. in one hour, the serum alkaline phosphatase 14 units, and plasma-proteins 7·8 gm. per 100 ml. (albumin 4·0 gm., globulin 3·8 gm.). Tests of lacrimation and perspiration were normal. Sternal marrow biopsy showed polymorphonuclear cells 23 per cent., lymphocytes 11 per cent., eosinophils 2 per cent., transitional neutrophils 9 per cent., metamyelocytes 7 per cent., neutrophil myelocytes 16 per cent., eosinophil myelocytes 1 per cent., plasma cells 4 per cent., haemocytoblasts 1 per cent., and normoblasts A 1 per cent., B 2 per cent., C 23 per cent. The marrow appeared to be hypoplastic. X-rays showed very advanced rheumatoid arthritis.

In view of the leucopenia and the rapid deterioration in the remaining eye, splenectomy was advised as offering a slender chance to preserve the eye, and was performed on April 5, 1949. There was a small patch of perisplenitis, but no adhesions. The spleen weighed 423 gm. The texture was firm, but not grossly abnormal. Microscopically there was atrophy of the Malpighian corpuscles and hyaline degeneration of the arterioles. There was endothelial-cell proliferation, dilatation of the sinuses, and no evidence of phagocytosis. There was a small pulmonary embolus on the third post-operative day, but otherwise the patient

recovered without complications. Five days after the operation her mouth was normal for the first time for three months, and the shoulders were less painful; they soon became free of pain. There was subjective, but no objective, improvement in the eye. There was no dramatic change in the leucopenia, but the white cells returned to low normal levels. In December 1949 she looked and felt very well. There had been no return of the ulcers in the mouth, and all the

TABLE III

	Date	Haemoglobin %	Red blood-cells (millions per c.mm.)	White blood-cells: per c.mm.	polymorphs %	eosinophils %	basophils %	lymphocytes %	monocytes %	Platelets (per c.mm.)
Pre-operative	1935	..	..	6,800	..	..	..	..	..	..
	3. 3.49	78	4·30	2,500	56	1	..	33	10	..
	5. 4.49	84	4·70	3,000	43	1	1	33	22	140,000
Operation	5. 4.49	..	..	..	..	..	..	..	..	..
Post-operative	7. 4.49	68	3·80	3,800	57	..	..	28	15	850,000
	25. 5.49	74	4·50	4,100	25	11	..	48	16	..
	1. 9.49	76	4·97	5,000	35	5	..	44	16	..
	14.12.49	70	4·88	4,500	69	3	..	20	8	..

joints were painless. The eye was not satisfactory. She could still recognize light and colour, but the episcleritis had spread and a ciliary staphyloma had formed. The eye had the appearance of scleromalacia perforans. Except for the eye condition she was as well as could be expected in her crippled state. The improvement in the blood picture was maintained (Table III).

Summary. A single woman aged 52 years was completely crippled with rheumatoid arthritis, which had begun 29 years before. A hypopyon ulcer developed in the right eye, which was excised later for panophthalmitis. Severe episcleritis followed in the left eye, and she got painful ulcers in the mouth. There was splenomegaly and leucopenia. Splenectomy led to rapid cure of the ulcers in the mouth and a partial arrest of the process in the remaining eye. The white blood-cells returned to low normal figures, and the improvement was maintained one year later, when she could still appreciate light in her eye.

Case 4. J. M., a single woman aged 36 years, was admitted to hospital on July 18, 1949, after a recent haematemesis. Joint pains were first noticed when she was 13 years old, and at the same time she began to have deformity in her hands. There was a further exacerbation in 1938, 12 years later, and the patient believes that this was the first time the enlarged spleen was noticed. By 1942 there was severe deformity in the hands, and she had a hypochromic anaemia (haemoglobin 58 per cent.), but she was able to lead a fairly normal life with physiotherapy and with iron preparations for her anaemia. In May 1946 she had a small ulcer over the left lateral malleolus, and despite routine treatment this ulcer continued to break down and was still present on her admission three years later. In August 1947 she was admitted to hospital with a relapse of the arthritis and severe anaemia. At that time the spleen was easily palpable, and the ulcer was present on the leg. Enlargement of the liver was not noted. The haemoglobin was 32 per cent., and leucopenia was recorded for the first time (Table IV). The plasma-proteins were 5·73 gm. per 100 ml. (albumin 3·42 gm.,

globulin 2·31 gm.). The anaemia was treated by blood transfusion. In February 1949 she had her first haematemesis, and on her admission to hospital hepatic enlargement and ascites were noted. She recovered after blood transfusion, but further haematemesis occurred in July and led to her admission to St. Thomas's Hospital. She had had no other serious illnesses. Her grandfather and

TABLE IV

	Date	Haemoglobin %	Red blood-cells (millions per c.mm.)	White blood-cells: per c.mm.	polymorphs %	eosinophils %	basophils %	lymphocytes %	monocytes %	Platelets (per c.mm.)
Pre-operative	19. 4.44	62	3·50	6,500	55	2	1	28	14	..
	(T) 27. 8.47	56	3·40	3,700	40	2	2	36	20	..
	21. 2.49	50	3·30	1,700	40	8	..	34	18	..
	(T) 8. 8.49	74	3·90	1,700	34	13	..	50	3	78,000
	18. 8.49	..	..	1,800	32	9	1	54	4	..
Operation	18. 8.49	..	..	..	..	..	..	..	..	..
Post-operative	23. 8.49	86	4·60	9,100	76	1	..	21	2	971,000
	22. 9.49	80	..	7,300	73	3	1	17	6	..
	4.11.49	100	..	9,000	60	2	..	34	4	..
	8. 5.50	96	4·90	9,600	63	3	..	30	4	..

(T) = Transfusion.

an aunt had suffered from rheumatoid arthritis. On examination she was pale and wasted, and looked extremely ill. There was a regular tachycardia and a loud, blowing systolic murmur was heard over the praecordium. The jugular venous pressure was raised 10 cm. above the sternal angle, and there were basal crepitations and some peripheral oedema. Ascites was present; the liver was palpable two inches, and the spleen four inches, below the costal margins. The epitrochlear, axillary, and inguinal lymph glands were enlarged. There was marked deformity of the hands, and the other joints showed peri-articular thickening and slight limitation of movement. An indolent ulcer, one inch across, was present on the left shin. The blood-pressure was 130/60; the urine contained no abnormal constituents. A blood count showed red cells 1,600,000 per c.mm. and haemoglobin 21 per cent., and after blood transfusion the signs of cardiac failure and the ascites disappeared. There was leucopenia and thrombocytopenia (Table IV). The erythrocyte sedimentation rate was 90 mm. in one hour; the Wassermann reaction was negative, thymol turbidity 3 units, serum alkaline phosphatase 7 units, icteric index 5 units, and plasma-proteins 5·95 gm. per 100 ml. (albumin 2·7 gm., globulin 3·25 gm.); the urine contained urobilinogen 1·5 mg. per 100 ml. Sternal marrow biopsy showed polymorphonuclear cells 1·4 per cent., transitional neutrophils 13·4 per cent., metamyelocytes 6 per cent., neutrophil myelocytes 10 per cent., eosinophil myelocytes 2·6 per cent., lymphocytes 4 per cent., monocytes 1·2 per cent., eosinophils 1·2 per cent., plasma cells 0·8 per cent., normoblasts A 3 per cent., B 8·4 per cent., C 47 per cent., and megaloblasts 1 per cent. There was an actual and relative normoblastic hyperplasia, and maturation arrest was present in the white-cell series. A barium swallow showed a large diverticulum at the lower end of the oesophagus, which was probably the source of the gastro-intestinal bleeding. X-rays of the hands showed the typical changes of advanced rheumatoid arthritis.

In view of the panhaemocytopenia, splenectomy was performed on August 18, 1949. The operation was very difficult because the spleen was adherent to the

under surface of the diaphragm, all the adhesions being very vascular. Owing to the technical difficulties a liver biopsy was not obtained. The spleen weighed 1,254 gm.; microscopically it showed slight generalized fibrosis of the entire splenic pulp, with an occasional peri-ellipsoidal haemorrhage, and a diffuse eosinophilic infiltration throughout the sinuses. All the Malpighian bodies showed active germinal centres, and were enlarged and very prominent. There was good initial recovery from the operation, but she later developed a subphrenic abscess, which was drained on September 20, 1949. The white blood count returned to normal at once, and this improvement has been maintained. The leg ulcer had healed with rest in bed, and for the first time remained healed. She was last seen on May 8, 1950, when she was looking and feeling very well. She was doing a full day's work, and said she felt better than she had done for years. The arthritis was quiescent, the leg ulcer was soundly healed, and the blood count was normal (Table IV).

Summary. A single woman, aged 36 years, had had rheumatoid arthritis for 23 years and splenomegaly for 11 years. Hypochromic anaemia had recurred during the last seven years, and there had been a chronic leg ulcer and leucopenia for three years. She was admitted after a second haematemesis with severe anaemia, cardiac failure, and ascites. The liver was enlarged; biochemical tests suggested cirrhosis, but the clinical picture was confused by the presence of a large diverticulum at the lower end of the oesophagus. The spleen was removed with difficulty owing to vascular adhesions. Recovery was complicated by a subphrenic abscess. Nine months after operation she was very well, and the leg ulcer remained healed. There was no ascites; the liver was still enlarged, but there was no other evidence of cirrhosis, and the gastro-intestinal bleeding had not recurred. The blood count was normal.

Discussion

In our first three cases nothing in the clinical or histological findings suggested a dual pathology. In Case 4 the association of hepatomegaly, ascites, and haematemesis make it reasonably certain that the patient had hepatic cirrhosis with portal hypertension, though unfortunately we were unable to confirm the fact by biopsy. It should be noted, however, that splenomegaly was present for about 10 years before any of the signs of cirrhosis, the clinical picture being similar to Banti's (1894) original description of his syndrome. While it seems certain that this patient eventually had cirrhosis, the clinical and histological findings suggest that the splenomegaly was not purely of the congestive type, and that we are justified in regarding it as partly due to the reticulo-endothelial hyperplasia of rheumatoid arthritis. Hatch (1945) reviewed 12 previous cases of Felty's syndrome, and presented three cases of his own. He found that in at least four of these 15 patients the splenomegaly was due to a pathological process unconnected with rheumatoid arthritis. In the remainder the spleen showed histological changes similar to those seen in our patients. The organ maintains its normal basic structure. The sinusoids are dilated, and the lining endothelial cells show evidence of hyperplasia. The pulp sometimes shows an increase of granulocytes and lymphocytes, and in some cases numerous

eosinophils. When these characteristics are taken together with the clinical findings there is little difficulty in separating cases of splenomegaly due to Felty's syndrome from those due to cirrhosis of the liver. We believe that the association of rheumatoid arthritis, reticulo-endothelial hyperplasia, and neutropenia constitutes a pathological entity, that such cases present a well-defined therapeutic problem, and that from the clinical point of view the term Felty's syndrome should therefore be retained.

Clinical features. The triad of findings outlined above are the essential features of Felty's syndrome. In all cases there is a considerable time-interval between the onset of arthritis and the development of splenomegaly and leucopenia. The interval was five years in Cases 1 and 2, and in Cases 3 and 4 about 20 years. The arthritis is therefore advanced, and permanent deformities of some joints are present. The hands in all our cases showed the typical appearances of advanced rheumatoid arthritis, with considerable destruction of the joint spaces, resulting in peculiar flail-like fingers. The degree of involvement of the other joints varied from complete ankylosis to slight peri-articular thickening. The articular manifestations were in every respect typical of advanced rheumatoid arthritis. The frequency of reticulo-endothelial involvement in rheumatoid arthritis varies in different accounts. In a series of 47 patients admitted to St. Thomas's Hospital for treatment, splenomegaly was present in 5 per cent. McCrae (1904) reported lymphadenopathy in 13 and splenomegaly in four of 110 cases; Coates and Delicati (1931) reported lymphadenopathy in 53 per cent. of cases; Dawson (1921) reported splenomegaly in 12 per cent., and Hench (1933) in 1 per cent. of all cases. The discrepancy in these figures is probably due to difference in the criteria with which clinical signs are assessed and in the diligence with which they are sought. But the figures quoted show that lymphadenopathy and splenomegaly are not infrequent findings in rheumatoid arthritis, though the full picture constituting Felty's syndrome is less frequently seen. The figures given refer to adult cases, but it is well known that reticulo-endothelial involvement occurs more frequently in children, constituting Still's disease. Schlesinger (1949) reported splenomegaly in 13 out of 20 cases of rheumatoid arthritis occurring in children under 10 years of age, lymphadenopathy being present in every case. This high incidence reflects the different type of reticulo-endothelial response which occurs in young people. Unlike Felty's syndrome, splenomegaly and lymphadenopathy in children usually occur in the acute phase of the disease, and the white-cell count shows a leucocytosis which only occasionally gives way to leucopenia. Except in these rare cases the clinical picture and the therapeutic problem in Still's disease are quite different from those in Felty's syndrome, and no further allusion to them will be made in the present paper.

Haematological features. The main feature which distinguishes Felty's syndrome from Still's disease and from uncomplicated rheumatoid arthritis is the blood picture. The pre-operative blood picture in all our cases showed anaemia, the very low figures in Case 4 being partly due to a haematemesis. It will be noticed that this patient had a fairly severe anaemia for many years before her first

haemorrhage. The figures for haemoglobin and red cells in Tables I to IV are not significantly below the values found in many cases of uncomplicated rheumatoid arthritis. But the average post-operative values showed a considerable rise, and it seems probable that the red cells were, to a lesser extent, sharing the fate of the white cells. Platelet depression was found in two cases, but in neither was there any evidence of a bleeding tendency. The white-cell count varied considerably, but in each case it was well below 3,000 per c.mm. at its lowest. In Cases 1 and 2 the lowest white-cell count before operation was about 800 cells per c.mm., in Case 3 2,000 per c.mm., and in Case 4 1,000 per c.mm. Some degree of leucopenia is, of course, seen in uncomplicated rheumatoid arthritis. McCrae (1904) found the white-cell count to be below 5,000 per c.mm. in six out of 110 cases, and Fleischacker and Lachnit (1940) found a count of below 5,000 per c.mm. in 11 out of 55 cases, but in none of the latter series was it below 3,000. In view of these findings the work of Wiseman and Doan (1939), who reported the first case of primary splenic neutropenia, is of special interest to us. In 1942 these authors described five cases of splenic neutropenia associated with splenomegaly and myeloid hyperplasia of the bone-marrow. Doan and Wright (1946) went further, and described patients with depression of all the blood elements as a manifestation of splenic over-action. They considered such conditions to be analogous to essential thrombocytopenia and familial haemolytic anaemia, the brunt of the splenic over-activity falling on one or more of the cellular elements of the blood so that anaemia, leucopenia, thrombocytopenia or any combination of these three may be found. The condition is sometimes primary, and sometimes secondary to well-recognized pathological processes of which splenomegaly is a feature. Doan (1949), in a recent review of 'hypersplenism', cited 94 cases of secondary splenic over-activity. Among the conditions mentioned by him in which this over-activity may occur are congestive splenomegaly, Gaucher's disease, the leukaemias, tuberculous splenomegaly, Hodgkin's disease, and Boeck's sarcoidosis (Doan and Wright, 1946, 1947; Dameshek, 1946; Mandelbaum, Berger, and Lederer, 1942; Scott, 1949).

Two schools of thought exist regarding the *modus operandi* of hypersplenism. The first suggests that the spleen exercises control over the normal maturation and delivery of the cells from the bone-marrow through some hormonal influence. This suggestion was originally made by Isaac (1912), and was supported by Krumbhaar (1926), and more recently by Dameshek (1944) who gave three reasons in its favour: leucocytosis follows splenectomy in normal animals and the removal of a normal spleen in man; leucopenia is often associated with splenomegaly from whatever cause; and in such patients there is evidence that their marrow hyperplasia and leucopenia disappear after splenectomy. The other school of thought follows the work of Wiseman and Doan (1939), who demonstrated by supravital staining that in the spleens of leucopenic patients with hypersplenism there is an excessive number of phagocytes containing ingested cells of the type of which the peripheral blood is being deprived. They attributed the bone-marrow picture to a normal compensatory hyperplasia which, however, is unable to effect the necessary accelerated delivery. Hirsch-

boeck (1946) discussed Felty's syndrome primarily with regard to the blood findings, and concluded that the evidence as yet was not sufficient to decide which of the two theories is correct. It seems probable that both factors may play a part. Whichever explanation is correct, it is agreed that the blood changes can be reversed by splenectomy, and it is this point that is important for our argument.

Additional clinical features secondary to hypersplenism. In various types of hypersplenism, whatever the original cause, certain associated clinical features have been recorded. Case 2 illustrates the severe buccal ulceration which is often present with neutropenia, and which was also a distressing feature in Case 3. These ulcers are often attended by severe pain, and may dominate the picture from the patient's point of view. They are frequently seen in cases of cyclic agranulocytosis, recurring with each decrease of the white cells (Leale, 1910; Sutton, 1911; Rutledge, Hansen-Pruss, and Thayer, 1930; Doan, 1932; Embleton, 1936; Barling, 1948; Fullerton and Duguid, 1949; Owren, 1949; Reimann and de Bardinis, 1949), and are also reported in cases of primary splenic neutropenia (Wiseman and Doan, 1942; Mallarmé, 1948; Erf and Fry, 1949). Corneal ulceration occurred in two of our cases and had not been reported previously, though Nyström (1946) and Ytrehus (1946–7) noted the presence of a disabling chronic conjunctivitis. Iritis, as is well known, occurs in 2 to 4·5 per cent. of cases of rheumatoid arthritis (Berens, Angevine, Guy, and Rothbard, 1938; Sorsby and Gormaz, 1946), but Duke-Elder (1938) did not mention rheumatoid arthritis as an aetiological factor in any of the conditions affecting the anterior chamber of the eye. Scleromalacia perforans, a late result seen in Case 3, is another recognized ophthalmic complication (Verhoeff and King, 1938; van der Hoeve, 1948). Two further cases of Felty's syndrome found in the records of St. Thomas's Hospital both had chronic keratitis, so the leucopenia would appear to be the aggravating factor leading to this serious disability. A further feature of one of our patients (Case 4) was ulceration of the leg. The ulcer was similar both in site and appearance to those seen in acholuric jaundice. There were small patches of pigmentation on the other leg which looked as though they might be precursors of further ulcers. Witts (1942) reviewed the literature in which leg ulcers had been associated with hypersplenism, and reported leg ulcers in two cases of thrombocytopenic purpura, in one of which the ulcers healed after splenectomy. Ulcers on the front of the shins have also been reported in acholuric jaundice, sickle-cell anaemia, splenic anaemia, and primary splenic neutropenia (Grégoire and Weil, 1929; Taylor, 1939; Cummer and La Rocco, 1940; Wiseman and Doan, 1942). No stress had been laid on this finding in cases of Felty's syndrome until Peden (1949) reported two cases in which leg ulcers were the outstanding feature. Similar ulcers had, however, been observed by Ytrehus (1946–7) and by Smith and McCabe (1948). The cause of the ulcers remains obscure. They are unrelated to depression of any one particular blood element, and one can only assume that there is vascular damage to an area especially susceptible to local devitalization.

It would appear that while joint involvement is universal in rheumatoid

TABLE V

Results of Splenectomy in Cases of Felty's Syndrome

	Patient		*Pre-operative state*						*Post-operative state*				
									Latest recorded blood picture				
Author	*Sex*	*Age (years)*	*History of arthritis (years)*	*Haemoglobin (%)*	*White cells (per c.mm.)*	*Platelets (per c.mm.)*	*Bone-marrow*	*Remarks*	*Haemoglobin (%)*	*White cells (per c.mm.)*	*Platelets (per c.mm.)*	*Time after operation*	*Results and comments*
Hanrahan and Miller, 1932	F	50	5	67	1,600	50,000	..	..	78	10,000	100,000	6 months	Marked improvement in arthritis and blood picture. DIED 18 months after operation (Fitz).
Craven, Jnr., 1934	F	40	5	78	3,720	200,000	..	Skin pigmentation present. General adenitis. Irregular fever. Eosinophilia 12 %	84	5,750	..	8 months	After 8 months the pigmentation had gone, but there was only slight improvement in the joints and general condition. DIED 14 months after operation (Fitz) from inanition and pneumonia.
Steinberg, 1942	F	45	7	78	1,500	..	Hyperplasia	Slight fever. General adenitis. Considerable loss of weight. Anorexia	78	4,000	..	3 weeks	No change in arthritis. Improvement in general health, with gain in weight and subsidence of fever. Anorexia continued.
Gyntelberg, 1942	F	56	23	75	1,000	197,000	Hypoplasia	Frequent infections in preceding 2 years	68	8,700	..	3 weeks	DIED from septicaemia 5 weeks after operation. Spleen was of 'congestive' type.
Trolle and Trolle, 1943	M	66	9	67	2,000	90,000	Hyperplasia with maturation arrest	Recurrent anaemia for 20 years which responded normally to iron	100	8,270 (12,500 15 months later)	..	4 months	Quite well 15 months later. Histologically the spleen contained *amyloid deposits*. Sternal marrow normal 4 months later.
Dameshek, 1944	F	..	15	..	900	100,000	Maturation arrest	Recurrent disabling infections and menorrhagia	Details not given				Leucocytes returned to normal. There were no further infections, and the menorrhagia ceased.
Zimmer, 1945	F	30	4	55	1,500	106,000	Hyperplasia with maturation arrest	One sister has similar disorder and three other relatives had rheumatoid arthritis	95	6,500	675,000	19 months	Improvement in joints, general condition, and white-cell count, maintained 19 months later.
Hirschboeck, 1946 (1)	F	35	3	68	850	130,000	Hyperplasia; maturation arrest	All forms of medical treatment tried without effect	100	8,500	276,000	5 years	Alive and well 5 years later. Gain in general health, improvement in arthritis.
(2)	F	49	4	72	950	282,000	Slight hyperplasia	Typical case	..	5,000	..	5 days	Patient DIED 6 weeks later from portal thrombosis after a stormy post-operative course.

Nyström, 1946		M	43	6	76	1,700	179,000	Maturation arrest	Leucopenia first noticed 5 years before. Spleen not noticed until 6 months before. Conjunctivitis, stomatitis, and brown pigmentation of shins	78	5,400	259,000	3 months	After operation had meningitis, cured by sulphonamide therapy. Thereafter made a good general recovery, with moderate improvement in the joints.
Smith and McCabe, 1948	(1)	M	52	25	74	1,450	375,340	Hypoplasia	Splenomegaly present 5 years. Had numerous infections, including pneumonia twice and gonorrhoea twice	106	6,380	..	4 months	Only 4 months follow-up; said to be 'full of pep' and working better than for years.
	(2)	F	59	4	97	1,400	556,800	Hyperplasia with maturation arrest	Had leg ulcer for 6 months, and chronic eosinophilia	95	13,000	..	15 months	Still 6 per cent. eosinophilia in this high count. Unsatisfactory follow-up. 'I think she has made a marked improvement'—the comment of another physician.
Peden, 1949	(1)	M	59	15	71	3,750	350,000	Hyperplasia	Chronic leg ulcer for 1 year	83	3,100	..	4 months	Leg ulcer healed after operation; temporary improvement in the blood picture. Leucopenia returned, and patient DIED one year later, after the ulcer had recurred.
	(2)	F	50	10	37	3,600	300,000	Slight hyperplasia	Chronic leg ulcer for 8 months	98	12,900	390,000	22 months	Leg ulcer remained healed; improvement in white-cell count maintained.
Gauld, 1949		F	38	15	52	800	127,000	Maturation arrest	Arthritis quiescent 5 years, but persistent fever. Vesicovaginal fistula for 16 years	110	9,600	252,000	17 months	Relapse of arthritis 1 year later, but considerable improvement in general health, and leucopenia did not recur.
Doan, 1949		..	..	..	..	..	..	..	Reported six cases of Felty's syndrome among 270 splenectomies for hypersplenism, but no details given.					
Cole, Walter, and Limarzi, 1949		..	..	..	..	..	..	..	Reported five cases among 87 splenectomies. In four the results were good, though in three there was no improvement in the arthritis. The symptomatic and haematological results were good.					

arthritis, the other tissues are affected to a varying degree; perhaps the most frequent extra-articular manifestation is involvement of the reticulo-endothelial system, leading to lymphadenopathy and, less commonly, to splenomegaly. At a later stage of the disease manifestations of hypersplenism may appear, as they may in any process where splenomegaly is a long-standing feature. The hypersplenism chiefly affects the granular leucocytes, leading to neutropenia, lowered tissue resistance, and various ulcerative conditions. This is Felty's syndrome.

Treatment. In 1932 Hanrahan and Miller recorded the first splenectomy in a case of Felty's syndrome. It was done empirically, and they reported satisfactory results, with an improvement in the blood picture and in the joints. Craven (1934) reported a further case, with similar initial results; but his patient soon relapsed, and the white-cell count returned to the leucopenic state. Fitz (1935) followed up these two cases, and found that both patients had died within 18 months of operation. Steinberg (1942), while reviewing the literature of splenectomy, reported one case of his own in which there was a good initial response, but later the leucopenia returned. More recently Zimmer (1945), Hirschboeck (1946), Smith and McCabe (1948), and Peden (1949) have reported a more favourable eventual outcome of treatment by splenectomy (Table V).

The effect of splenectomy on our patients will be considered in relation to the various components of the syndrome. In only one case was there an undoubted and measurable improvement in the joints, but in this patient the post-operative change was quite dramatic (Case 1). The slight changes in the other cases were due, we felt, to the improvement in the general well-being of the patient, and our results and those recorded in the literature make it clear that splenectomy should not be regarded as a treatment for the joint condition itself. The poor results may be largely due to the advanced state of the arthritis, and thus our opinion is not necessarily incompatible with the results claimed by Bach and Savage (1940). There was an immediate post-operative increase in white blood-cells in every case, and this increase has so far largely been maintained. Cases 1 and 2 also showed a significant increase in the haemoglobin and red-cell figures. Case 4 could not be judged post-operatively from this point of view because of the complications of haemorrhage and transfusion. But her average haemoglobin level three months after the operation was considerably higher than it had been for many years. Two patients in whom the platelet count was low showed a return to normal values, and there was a post-operative thrombocytosis in every case. In Case 4 the platelets increased to nearly 1,000,000 per c.mm. In Case 3 it will be noticed that the bone-marrow was hypoplastic. This is the antithesis of the usual bone-marrow picture, as seen in our other cases and stressed by Doan (1949) in his description of hypersplenism. Smith and McCabe (1948) described one case in which splenectomy was done in spite of a hypoplastic marrow, with a successful result and the return of a normal blood picture. They also cited two other cases, the first presented by Salzer, Ransohoff, and Blatt (1945) and the second by Alt (1945), in which the bone-marrow was not hyperplastic, and in which splenectomy was curative. It appears possible that the hypoplastic picture may represent an exhaustion of the bone-marrow which

is reversible in its early stages. The decision to operate in our case was based on the hopeless outlook confronting the patient, who was rapidly becoming blind as well as completely bedridden. Perhaps the most remarkable effect of splenectomy is on the secondary manifestations of neutropenia. The two patients in whom there were buccal manifestations showed rapid improvement. In both cases the chronic ulcers which had been present for months healed within a few days, and the painful stomatitis subsided equally quickly. A similar rapid response to splenectomy has been noted in other cases of hypersplenism with neutropenia, notably in primary splenic neutropenia and in some cases of cyclic agranulocytosis (Nordenson and Röden, 1941; Fullerton and Duguid, 1949; Erf and Fry, 1949). In Case 3, in whom the condition was too far advanced to allow much success, there appeared to be a slight improvement of vision in the remaining eye, which has so far been preserved from enucleation, though this step had previously seemed inevitable. The eye now shows the appearance of scleromalacia perforans. The leg ulcer in Case 4 had healed before operation while the patient was resting in bed. Previously it had always broken down after she began walking, but so far it has remained healed. Peden (1949) reported the healing of a similar ulcer after splenectomy when all other methods of treatment had failed.

Acknowledgements

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Summary

We have endeavoured to show that the triad of findings, rheumatoid arthritis, splenomegaly, and neutropenia, constitute a clinical entity which may reasonably be called Felty's syndrome. Many other features may be added to these findings and so produce a variable clinical picture. It is considered that the syndrome is merely a peculiar variant of rheumatoid arthritis, and not a separate entity. The feature on which we have laid most emphasis is the neutropenia. We consider that this feature is entirely secondary to hypersplenism, which may occur in any disease in which splenomegaly is a feature. The therapeutic problem in Felty's syndrome is dependent on the hypersplenism. We feel that, provided there are not other associated diseases which would contra-indicate operation, splenectomy should be carried out in all cases. The effect of splenectomy is to restore the white-cell count to normal and, as a result, to clear up the associated infective processes and to improve the general health of the patient. All our four patients have now been followed up for over a year, and the beneficial results have been maintained. In every case the most striking feature has been the improvement of general health.

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APLASTIC ANAEMIA[1]

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Introduction

Aplastic anaemia, which was first described by Ehrlich in 1888, can be defined as a progressive anaemia with leucopenia and thrombocytopenia but without evidence of increased blood destruction. Within recent years an increasing number of cases of this disease have been reported, but, in view of the wide variations in its natural history and pathology, it seems that several different conditions have been included. They have in common the classical blood picture and the characteristic lack of response to any remedy but blood transfusion. Recent therapeutic developments in haematology make it preferable that this group of conditions should continue to be classified as the aplastic anaemias, despite temporary favour gained by the term 'refractory anaemia' (Bomford and Rhoads, 1941). In the present paper it is proposed to discuss briefly some salient features of the aplastic anaemias, and to review 25 cases of the disease in patients admitted to the Royal Victoria Infirmary, Newcastle, during (with one exception) the last 10 years; cases in which the patients recovered will be described in detail.

Aetiology. Drugs and other toxic substances have been recognized in increasing number as a cause of aplastic anaemia since benzol was first incriminated by Santesson (1897). Probably organic arsenicals, gold compounds, and radioactive substances have recently supplanted benzol as the commonest offenders. Numerous substances have been adduced in individual case reports, and important recent additions to the list include sulphonamides (Meyer and Perlmutter, 1942), mepacrine (Custer, 1946; Parmer, 1948), streptomycin (Corelli, 1947), tridione (Mackay and Gottstein, 1946; Harrison, Johnson, and Ayer, 1946; Carnicelli and Tedeschi, 1948), thorotrast (Spier, Cluff, and Urry, 1947), and 'mesantoin' (Bloom, Lynch, and Brick, 1948). In one of the cases to be reported below colchicine appears to have been the cause. Other factors postulated as a cause of aplastic anaemia include pituitary insufficiency (Bloom and Bryson, 1948). Parasitic infestations may also play a part, and hookworms have been suggested as a cause (Stransky and Quintos, 1947). Patients in whom no toxic causal agent can be discovered fall into the idiopathic group.

Clinical picture. Ehrlich (1888) originally described the condition as an acute illness occurring in adolescents and young adults, but it is now evident that it can occur at any age, although in the older age-groups it tends to be more chronic. Epistaxis, uterine haemorrhage, and bleeding into the skin, mucous membranes, and retina are important features; signs of an infective process,

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particularly agranulocytic angina, are also common. In many patients, however, the clinical picture is simply that of a progressive anaemia; the presence of these additional signs usually indicates a rapid course, while in their absence the illness is frequently insidious and slow. Although no absolutely distinct division can be made, it is therefore clear that patients with aplastic anaemia can be divided on clinical grounds into acute and chronic groups, and this division has been made in the present series. Splenomegaly, atrophic glossitis, and neurological signs (except as a result of haemorrhage) do not occur.

Blood and bone-marrow. As already mentioned, the characteristic triad of anaemia, leucopenia, and thrombocytopenia is invariable. There is considerable variation in the marrow picture. In acute cases particularly the marrow may consist mainly of fat and fibrous tissue, although a careful search may reveal islands of functioning marrow, thus explaining the occasional appearance of reticulocytes in the circulating blood (Bomford and Rhoads, 1941). In other individuals the marrow is hyperplastic, with a pronounced maturation defect (Rhoads and Miller, 1938; Thompson, 1934); in others again it is partially mature and cellular (Bomford and Rhoads, 1941).

Diagnosis. The diagnosis of aplastic anaemia is made on the blood and marrow findings mentioned above. Confusion may arise with agranulocytosis, thrombocytopenic purpura, aleukaemic leukaemia, splenic panhaematopenia (Doan and Wright, 1946), and infiltration of the marrow by neoplastic secondary deposits. A single marrow biopsy by aspiration is not sufficient for a positive diagnosis, and surgical biopsy, for example from the iliac crest, is recommended. In aleukaemic leukaemia particularly there may be islands of gelatinous degeneration in the marrow, and aspiration of tissue from one of these areas may lead to a mistaken diagnosis of aplastic anaemia. Two such cases have recently been seen in the Royal Victoria Infirmary; both patients were treated at first as cases of aplastic anaemia, but it later became evident that they were suffering from myeloid leukaemia (R. B. Thompson, personal communication).

Treatment. The mainstay of treatment is blood transfusion (Wintrobe, 1946), which has been known to keep a patient alive for nine years (Kark, 1937). No drug has yet been proved to be of value; reports of improvement following folic acid therapy (Gendel, 1947) have not been substantiated (Wilkinson, 1948). It is too early yet to assess the value of marrow transplantation (Morrison and Samwick, 1940).

Prognosis. Recovery from aplastic anaemia is very rare, although the prognosis in the cases due to drugs is somewhat better than in the idiopathic disease. Wintrobe (1946) found reports of recovery in 18 cases due to organic arsenicals, and added two personally observed cases in which the patient recovered out of a total of seven. Up to 1939 six patients suffering from the idiopathic disease had recovered (Wintrobe, Stowell, and Roll, 1939), and in later years Wintrobe (1946) was able to add another, although at the same time he was careful to point out that usually 'death ensues in six weeks, or life may linger for as long as six months'. A recent example of recovery has been reported by Lyndrup (1946).

The Present Series

With one exception, a case previously reported by one of us (Boon, 1938), all the 25 patients in this series were admitted to the Royal Victoria Infirmary between January 1, 1940, and December 31, 1949. Owing to war-time difficulties some case records are scanty and investigations inadequate, and it may be that considerably more patients have been admitted than the 25 to be reviewed

TABLE I

Case number	*Age (years)*	*Sex*	*Aetiology*	*Type*	*Blood picture*	*Marrow*	*Result*	*Period of survival after admission*
1	50	M	Neoarsphenamine	Chronic	Normocytic	Not examined	Recovery	..
2	50	F	Gold	Chronic	Macrocytic	Hyperplastic	Recovery	..
3	46	F	Gold	Chronic	Macrocytic	Aplastic	Recovery	..
4	46	F	Gold	Acute	Normocytic	Hypoplastic	Death	3 days
5	67	F	Gold	Acute	Macrocytic	Aplastic	Death	4 days
6	28	M	X-rays	Acute	Macrocytic	Hypoplastic	Death	3 months
7	35	F	Colchicine	Acute	Macrocytic	Aplastic	Death	8 months
8	44	F	Idiopathic	Chronic	Normocytic	Not examined	Death	5 years
9	36	F	Idiopathic	Chronic	Macrocytic	Hypoplastic	Death	2 years
10	60	F	Idiopathic	Chronic	Macrocytic	Hyperplastic	Death	2 months
11	56	M	Idiopathic	Chronic	Macrocytic	Aplastic	Death	2 weeks
12	30	M	Idiopathic	Chronic	Macrocytic	Hypoplastic	Death	2 years
13	21	M	Idiopathic	Chronic	Macrocytic	Hypoplastic	Recovery	..
14	70	M	Idiopathic	Chronic	Macrocytic	Hyperplastic	Death	2 months
15	74	M	Idiopathic	Chronic	Macrocytic	Aplastic	Death	5 days
16	63	M	Idiopathic	Chronic	Normocytic	Aplastic	Recovery	..
17	67	F	Idiopathic	Chronic	Normocytic	Aplastic	Death	3 weeks
18	17	F	Idiopathic	Acute	Macrocytic	Aplastic	Death	6 weeks
19	19	F	Idiopathic	Acute	Normocytic	Hypoplastic	Recovery	..
20	24	F	Idiopathic	Acute	Normocytic	Hyperplastic	Death	2 weeks
21	21	M	Idiopathic	Acute	Macrocytic	Aplastic	Death	2 weeks
22	15	M	Idiopathic	Acute	Normocytic	Hyperplastic	Death	2 weeks
23	62	M	Idiopathic	Acute	Normocytic	Hypoplastic	Death	4 months
24	60	M	Idiopathic	Acute	Macrocytic	Hypoplastic	Death	1 month
25	13	M	Idiopathic	Acute	Macrocytic	Hypoplastic	Under treatment	

below. All cases have been excluded in which the diagnosis has not been substantiated beyond reasonable doubt. Sixteen of the patients have been seen by one or both of the authors at some stage; details concerning the others have been taken from the Hospital in-patient records. Cases have been divided into acute and chronic groups by means of the criteria described above; Table I gives a general outline of the series.

Incidence and aetiology. Twelve of the patients were female and 13 male. The age- and sex-incidence is shown in Fig. 1. From this it is evident that there is no specific age-incidence of the disease, except that it is uncommon in childhood. The youngest patient in the series was 13 and the oldest 74 years old. In four cases the causal agent appeared to be gold, administered in three cases for rheumatoid arthritis and in one (in 1940) for osteoarthritis. Colchicine was the apparent cause of the anaemia in one instance (Case 7, to be reported in detail below). In one other case, also to be reported fully, the disease appeared to be due to an organic arsenical. Another patient developed typical aplastic anaemia after a course of general X-ray baths given as treatment for lymphosarcoma. In the remaining 18 cases no specific agent could be incriminated on careful inquiry, and they must therefore be classified as idiopathic. The age and sex distribution of the idiopathic cases is shown in Fig. 2; the incidence of the acute and chronic cases is given in Fig. 3. These figures suggest that idiopathic

aplastic anaemia and acute aplastic anaemia are commoner in the 10–30 and 60–70 age-groups, although the numbers are so small that they cannot be considered statistically significant.

Clinical picture. 1. *Symptoms.* All the patients complained of the general symptoms of anaemia in varying degree. Weakness, tiredness, lack of energy,

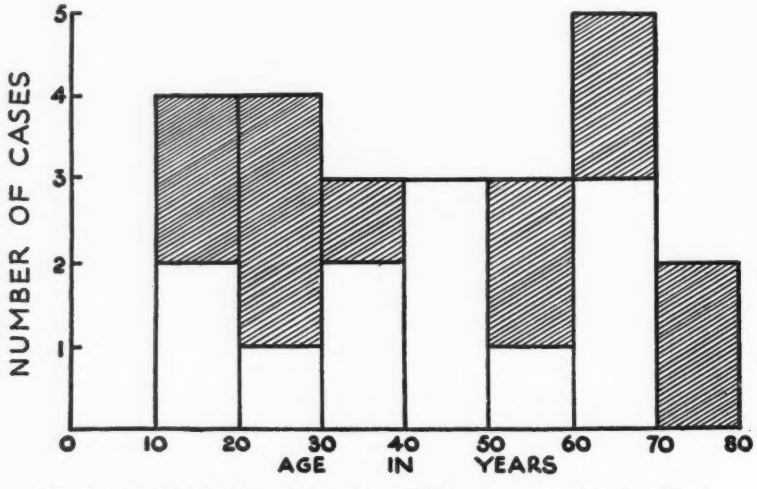

FIG. 1. Age-distribution of the series. White columns = female patients, dark columns = male patients.

breathlessness on exertion, palpitations, swelling of the ankles, and increasing pallor were all mentioned by the majority, and one elderly man gave a history of recent angina of effort. Severe sore throats were present in three cases. Twelve patients had haemorrhage; this took the form of epistaxis in eight cases, and four women who had epistaxis also had metrorrhagia. Two other women had metrorrhagia alone. One patient had profuse bleeding from the gums, and another haemoptysis and haematuria. All the 12 patients in whom haemorrhage occurred had also noticed either spontaneous bruising of the skin or bruising on slight trauma. The duration of symptoms prior to admission to hospital varied between one week (in one case) and five months (in one case), the average being seven to eight weeks. The period was as a rule much shorter in the acute cases. In the latter the loss of blood, in combination with the rapid failure of the bone-marrow, led to such rapid exsanguination that the patients were almost *in extremis* by the time they were admitted. In Case 19 the haemoglobin was 13 per cent. (1·8 gm. per 100 ml.) and in Case 24 it was 16 per cent. (2·2 gm. per 100 ml.) on admission. In the chronic cases, though there was rarely any bleeding, the condition was equally dangerous owing to its insidious character. Several patients were submitted to long periods of treatment with iron and liver extract at home before being referred to hospital; in Case 12 the haemoglobin was 9·5 per cent. (1·3 gm. per 100 ml.) on admission.

2. *Physical signs.* In all cases general signs of severe anaemia (pallor of the skin, conjunctivae, and mucous membranes) were evident. Purpuric spots in the

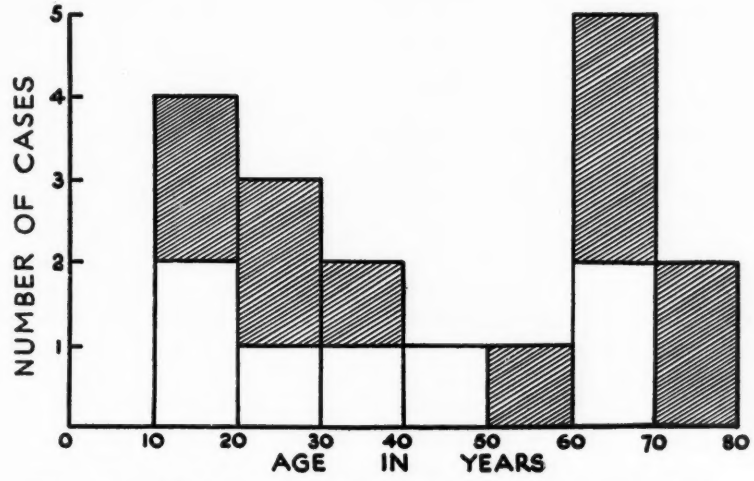

FIG. 2. Age-distribution of the idiopathic cases. White columns = female patients, dark columns = male patients.

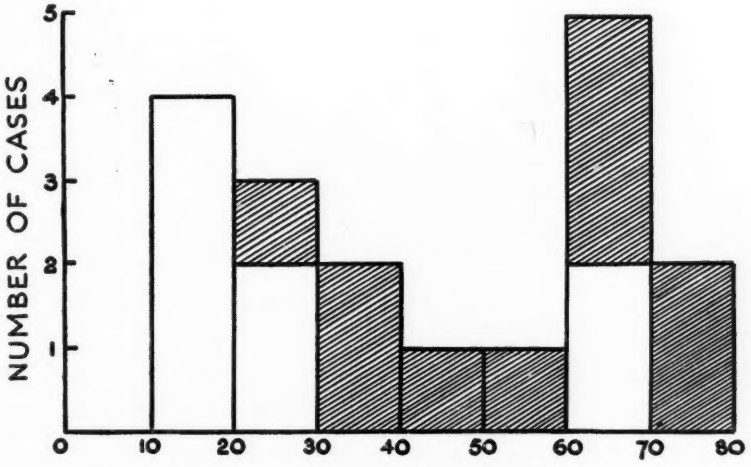

FIG. 3. Age-distribution of acute and chronic idiopathic cases. White columns = acute cases, dark columns = chronic cases.

skin were discovered in all 12 patients who complained of haemorrhage, and in three others, and retinal haemorrhages were noted in 10; the majority of these patients were in the acute group, but haemorrhagic phenomena were present in some of the chronic cases in whom the degree of anaemia was severe; they

were infrequent at higher haemoglobin levels, in spite of the low platelet count. Severe agranulocytic angina was found in three patients who complained of sore throat; three others had necrotic ulcers on the tonsils, and two had ulcerative stomatitis. Pyrexia, usually 100° to 103° F., was present in all the acute cases.

TABLE II

Peripheral Blood Findings on Admission

Case number	*Haemoglobin* (%)	*Red cells (millions per c.mm.)*	*Colour index*	*Mean corpuscular volume* (c.μ)	*White cells (per c.mm.)*	*Platelets (per c.mm.)*	*Reticulocytes* (%)
1	23	1·38	1·02	..	2,200	38,000	< 1
2	61	2·60	1·38	..	5,400	..	2·8
3	27	1·05	1·29	109·5	1,100	33,000	0·8
4	56	3·22	0·87	..	900	138,000	< 1
5	40	1·82	1·10	..	1,000	..	< 1
6	30	1·36	1·10	94	600	< 40,000	1·4
7	23	1·19	0·97	86	1,700	80,000	< 1
8	34	1·80	0·94	..	2,800	..	1·5
9	42	1·80	1·10	..	3,000	..	< 1
10	44	2·40	0·92	..	1,200	..	< 1
11	31	1·03	1·50	..	2,400	..	< 1
12	9·5	0·44	1·10	113·7	2,200	< 40,000	< 1
13	37	1·44	1·28	115·1	3,000	40,000	1·0
14	20	0·92	1·09	..	1,600	..	1·0
15	24	1·14	1·05	100	1,900	..	..
16	37	1·83	1·01	90	2,900	50,000	1·2
17	30	1·58	0·95	..	2,000	100,000	< 1
18	22	1·00	1·10	..	1,200	..	< 1
19	13	0·68	0·96	87	2,300	< 40,000	1·8
20	37	1·35	1·00	..	4,000	..	< 1
21	27	1·27	1·06	..	2,000	..	1·2
22	22	1·10	1·00	..	1,800	< 40,000	< 1
23	30	1·66	0·90	..	3,100	67,000	< 1
24	16	0·64	1·25	..	2,200	< 40,000	< 1
25	30	1·10	1·36	94·5	2,200	126,000	< 1

Splenomegaly was present only in one patient, who had generalized lymphosarcoma, and was due to the latter condition.

Peripheral blood findings. The blood counts on admission are shown in Table II. All the patients showed anaemia and leucopenia. In the acute cases the haemoglobin level on admission varied between 13 per cent. (1·8 gm. per 100 ml.) and 56 per cent. (7·6 gm. per 100 ml.), the average being 28 per cent. (3·9 gm. per 100 ml.). In the chronic cases the haemoglobin was 9·5 per cent. (1·3 gm. per 100 ml.) in one case and 61 per cent. (8·5 gm. per 100 ml.) in one case, the average being 33 per cent. (4·6 gm. per 100 ml.). A haematocrit test was performed in nine of the most recent cases only, and showed macrocytosis (mean corpuscular volume over 90 c.μ) in six cases and normocytosis in three. In all cases a red-cell count was done and, if a colour index greater than 1·01 is taken as the criterion, macrocytosis was present in 16 cases, the other nine patients having a normocytic anaemia. There was no correlation between the acuteness of the disease and macrocytosis; in seven acute cases the anaemia was macrocytic, in five normocytic; in nine chronic cases it was macrocytic, and in four normocytic. The total white-cell count varied between 600 cells per c.mm. in one case

and 5,400 cells per c.mm. in one, the average being 2,100 per c.mm. In the 18 patients in whom there is a record of a differential white-cell count, polymorphonuclear leucopenia and relative lymphocytosis were invariable. Platelet counts were done in 14 cases, and in all there was thrombocytopenia, the count in the majority being recorded as 40,000 cells per c.mm. or less, although in one acute case a single count of 138,000 per c.mm. was noted. The reticulocytes were estimated in 24 cases; in 16 the initial count was recorded as less than 1 per cent., in seven it was between 1 and 2 per cent., and in one between 2 and 3 per cent. In five patients who survived for more than a few days an occasional reticulocyte count of between 2 and 3 per cent. was recorded, and in three the count rose occasionally above 3 per cent.

Marrow findings. In 20 cases marrow biopsy was done by sternal puncture, and in five of these surgical biopsy of the iliac crest was performed. In three others the condition of the marrow was first recorded at autopsy, and in two patients (Cases 1 and 8) there is no information as to the state of the marrow. In five instances the marrow was hyperplastic with a maturation defect, in nine it was hypoplastic, and in nine completely aplastic. In no case was megaloblastic erythropoiesis recorded, as in the cases of so-called 'achrestic' anaemia (Israëls and Wilkinson, 1936). The condition of the marrow was confirmed at autopsy in eight cases. There was no correlation between the type of marrow picture and the clinical course of the disease.

Autopsy findings. Besides the characteristic bone-marrow changes, typical findings in the eight cases in which autopsy was performed included haemorrhages into the skin, serous membranes, and viscera, pharyngeal and general sepsis, and urinary infection. In one patient (Case 9), who survived for two years, additional findings were haemosiderosis and generalized skin pigmentation; she died from a transfusion reaction, and the kidneys showed the typical pathological appearance of the so-called 'transfusion kidney'.

Treatment. In the acute cases the dramatic clinical picture usually compelled admission to hospital at an early stage, but the admission of many of the chronic patients was delayed by empirical treatment at home. In 18 cases iron by mouth and/or injection of liver extract were tried, either in the earlier stages or after the patients had been revived by blood transfusion. In no case was there any sustained haematological response, although occasionally a temporary rise of reticulocytes to 3 per cent. was recorded without any parallel increase in red-cell and haemoglobin values. Our experience has confirmed Wintrobe's (1946) assertion that blood transfusion is the only effective treatment of the disease. Transfusion was carried out in 22 patients; in the other three, owing to their age, their general condition, and the technical difficulties, palliative treatment alone was given. Marrow transplantation (Morrison and Samwick, 1940) was carried out in two patients (Cases 16 and 25); they received on several occasions intrasternal injections of 2 ml. of marrow from a donor of identical genotype. One of these patients has recovered, and the other is recovering, but it is impossible to judge the value of this procedure because the progress of the disease is unpredictable, and because a sufficient number of exactly comparable

cases cannot be found for a controlled investigation. Marrow transplantation does not appear to reduce the need for blood transfusion, but may have some adjuvant value and can reasonably be tried whenever possible. Difficulties arising in treatment will be discussed later.

Complications. The most common complication of treatment was reaction to blood transfusion. This occurred in 14 cases, usually in the form of rigors, occasionally with headache and vomiting; one of the patients died of a clinically typical incompatibility reaction, although the blood administered appeared perfectly compatible. In all patients who were given transfusions over any length of time phlebothrombosis took place, but in three there was at some stage a definite thrombophlebitis which required intensive treatment in hospital, and one patient after transfusion developed a severe cellulitis of the arm. Another developed homologous serum jaundice, but made a good recovery. Two patients developed generalized pigmentation of the skin after attending for transfusion over a long period, and one of these had symptoms and signs suggestive of cirrhosis of the liver.

Results. 1. *Death.* Eighteen of the patients in this series died after periods of treatment varying from four days to five years; in four the disease was symptomatic, and in 14 idiopathic; in eight it was chronic, and in 10 acute. In the patients who died from the acute disease death commonly occurred within six weeks, although two patients who eventually died survived for four and eight months respectively. Five of the chronic sufferers died within three months, two survived for two years, and one for five years. Death was often due to a combination of haemorrhage and sepsis. In two cases it was due to bronchopneumonia, in two to cardiac failure, in one to cerebellar haemorrhage, in another to subarachnoid haemorrhage, and in another to a transfusion reaction.

2. *Recovery.* Six patients have recovered; in two gold was the aetiological factor, and in both these patients the disease was chronic. One chronic case was due to neoarsphenamine. In addition, recovery has taken place in two chronic idiopathic cases and in one acute idiopathic case. In view of the importance of these six cases, they are reported in detail.

Case Histories

Case 1. This case has been reported previously by one of the authors (Boon, 1938). A baker, aged 50 years, was admitted to the Royal Victoria Infirmary under the care of Dr. J. C. Spence on May 30, 1935, and gave a history of increasing pallor and breathlessness for two months; for a week before admission he had bruised easily. In 1926 he was found to have a positive blood Wassermann reaction. For the next nine years he was treated intermittently with injections of neoarsphenamine, a total of over 10 gm. being given prior to the onset of symptoms of anaemia. On examination he was pale, stuporous, and breathless. The skin showed a widespread purpuric rash and numerous ecchymoses, and he was almost blind from retinal haemorrhages. There were a few ragged ulcers in the oral mucosa. The spleen was not palpable. Apart from absent ankle-jerks, no other abnormal physical signs could be found. Blood examination showed haemoglobin 23 per cent. (3·2 gm. per 100 ml.), red cells 1·38 million per c.mm., colour index 1·02, white cells 2,200 per c.mm., platelets 38,000 per c.mm., and

reticulocytes 0·6 per cent. A differential white count showed polymorphonuclear leucopenia and relative lymphocytosis. The Wassermann reaction was positive. The serum-bilirubin was normal. X-rays of both femora showed no abnormality. Marrow biopsy was not performed. The patient's haemoglobin level fell rapidly to 18 per cent., and his condition became critical; ten blood transfusions, each of one pint, were given during the next three weeks. He then improved dramatically. The retinal haemorrhages and purpura disappeared, his vision was restored to normal, and he was discharged five weeks after admission. Subsequently he attended every three weeks for transfusion as an out-patient, one pint of blood being given on each occasion through a fine-bore needle. After one transfusion he had an epileptiform fit and developed a generalized urticaria, which subsided after two days. The patient had previously received blood from the same donor. In March 1936, owing to technical difficulty, transfusion was delayed; after several weeks the haemoglobin level began to rise. His reticulocytes rose to 6·3 per cent., and recovery thereafter was uninterrupted. No further transfusion was required, and three years later he was well and at work.

Comment. A case of chronic aplastic anaemia due to the administration of neoarsphenamine. The patient's condition on admission was regarded as hopeless. After blood transfusion he improved remarkably, and during the next nine months led a reasonably active life while attending as an out-patient for transfusion; eventually recovery was complete.

Case 2. A married woman, aged 50 years, was admitted to the Royal Victoria Infirmary under the care of Dr. Mason Bolam on May 7, 1940. Since the age of 20 years she had had attacks of asthma, which had become severe of late. At the age of 35 years she was found to be suffering from osteoarthritis. In 1939 her doctor gave her, as treatment for the latter condition, a course of 10 injections of a gold compound. Some months later she developed a crop of boils in both ears and on the vulva. This was followed by a generalized eczematous skin eruption, and she was admitted to hospital for treatment. On examination, in addition to the skin condition and signs of chronic asthma, she was evidently anaemic. There was no evidence of purpura or of bleeding; the spleen was not palpable. The throat was clean, and despite the condition of her skin and chest she had no fever. Blood examination showed haemoglobin 61 per cent. (8·5 gm. per 100 ml.), red cells 2·60 million per c.mm., colour index 1·38, white cells 5,400 per c.mm., and reticulocytes 2·8 per cent. There is no record of a platelet count or of a differential white count. A histamine test meal showed free HCl in the gastric juice. The serum-bilirubin and red-cell fragility were normal, and X-rays of both femora showed no abnormality. A sternal marrow biopsy showed a hyperplastic marrow with a maturation defect; pronormoblasts were numerous, normoblasts few in number. She received 10 ml. of 'campolon' intramuscularly each day for one week, but the reticulocyte count remained at 2 per cent., the haemoglobin fell to 53 per cent., and the white cells to 2,400 per c.mm. She was given a transfusion of the packed cells of one and a half pints of blood; her haemoglobin rose to 75 per cent., and since her skin condition had improved she was discharged. In view of her asthma and the skin condition, to avoid travelling, she was visited at her home by one of us (T. H. B.) and was given a transfusion of the packed cells of two pints of blood every fortnight. She dreaded each transfusion owing to the frequent, though mild, local and general reactions. For five months she was bedridden, but then gradually resumed normal activity; while in bed she had two small vaginal haemorrhages, but these did not recur.

In June 1942 her haemoglobin level rose spontaneously, and since that date no further blood has been given. Although moderately disabled by osteoarthritis and by periodic attacks of asthma, she has since lived a reasonably active life. In 1948 she had an attack of pancreatitis, and six months later cholecystectomy was performed after a typical attack of gall-stone colic. She made a good recovery from the operation, and when last seen on May 30, 1950, she felt well. A blood count showed haemoglobin 96 per cent. (14·2 gm. per 100 ml.), red cells 4·79 million per c.mm., colour index 0·96, white cells 6,700 per c.mm., platelets 420,000 per c.mm., and reticulocytes 1·6 per cent.

Comment. A case of chronic aplastic anaemia due to the administration of a gold compound for osteoarthritis. Despite a severe associated skin condition and repeated attacks of asthma, the patient received a transfusion fortnightly at her home for two years, and has made a good recovery. She has lived a reasonably active life for eight years, and has had no recurrence of anaemia.

Case 3. A married woman of 44 years was first seen in the out-patient department of the Royal Victoria Infirmary in 1943, suffering from a menopausal polyarthritis of rheumatoid type. She was given 12 weekly injections of a gold preparation, a total of 0·85 gm. being given, and about four months later the course was repeated. After this treatment her arthritis resolved almost completely, but about nine months later she began to lose energy, became tired, listless, and breathless, and was becoming pale. On March 19, 1945, she attended the out-patient department; a blood count showed haemoglobin 45 per cent. (6·3 gm. per 100 ml.), red cells 1·83 million per c.mm., and colour index 1·23. While awaiting admission she sustained a severe Pott's fracture and was admitted to the orthopaedic department. Her pallor increased steadily, and on April 16, 1945, she was transferred to a medical ward under the care of Professor F. J. Nattrass. At no stage had there been any haemorrhage. On examination she was mentally alert. There was severe pallor of the skin, conjunctivae, and mucous membranes; there were a few small purpuric spots in the skin, but no haemorrhages in the retinae, and the spleen was not palpable. Blood examination showed haemoglobin 27 per cent. (3·8 gm. per 100 ml.), red cells 1·05 million per c.mm., colour index 1·29, white cells 1,100 per c.mm., cell-volume 11·5 per cent., mean corpuscular volume 109·5 c.μ, platelets 33,000 per c.mm., and reticulocytes 0·8 per cent. Two sternal marrow biopsies revealed a completely aplastic marrow. The specimens consisted mainly of fat; haemopoietic cells were very scanty indeed, and the predominant nucleated cells were lymphocytes. She was given a transfusion of the packed cells of two pints of blood immediately, and further transfusions were given at intervals of a few days. On May 5 the haemoglobin level had risen to 87 per cent., and she was discharged. She attended again for transfusions, at first fortnightly, but later the interval was lengthened to three weeks and then to a month. On four occasions during the next nine months she had severe transfusion reactions, twice necessitating her admission to hospital for periods of 10 days. These reactions made her dread the transfusions, and emotional outbursts were frequent. In July 1946, after living a 'transfusion life' for more than a year, she began to have uterine haemorrhage; after seven weeks this became heavy and continuous, and she was admitted to hospital severely exsanguinated. By this time practically every superficial limb vein had become firmly closed by thrombosis, and the last two transfusions had been given into the left external jugular vein. At this stage one of us (J. N. W.) was called upon to give her transfusions. A 'drip' was erected successfully into the right external jugular vein, and on July 23, 1946, an emergency subtotal

hysterectomy was performed. Her recovery from the operation was uneventful, and she continued to attend at monthly intervals for further treatment. From December 1946 the intervals between transfusions were lengthened, and the last was given in August 1947. She has since been extremely well and has led a normal life. When she was last seen on May 23, 1950, her haemoglobin was 76 per cent. (10·6 gm. per 100 ml.), red cells 4·36 million per c.mm., colour index 0·87, white cells 2,700 per c.mm., and platelets 260,000 per c.mm.

Comment. A case of recovery from chronic aplastic anaemia in which gold was the causal agent. Transfusions were continued for two years and three months despite considerable technical and psychological difficulty. Subtotal hysterectomy was performed as an emergency operation when uterine haemorrhage threatened the patient's life.

Case 13. A naval rating, aged 20 years, was admitted to the Royal Victoria Infirmary under the care of Dr. C. N. Armstrong on October 6, 1943. In May 1943, while serving in the Navy, he had a very severe epistaxis and was admitted to a naval hospital. Although the original bleeding was stopped by packing the nose, severe haemorrhage recurred on three occasions during the next three months, and each time he required transfusion. In August he began to have bleeding from the gums. In September, after extensive investigation of the gastro-intestinal tract, an examination of the sternal marrow suggested a diagnosis of aplastic anaemia; the patient was invalided from the service and transferred to the Royal Victoria Infirmary. Further questioning failed to reveal any specific cause of the disease. On examination he was pale and breathless; there were a few purpuric spots in the skin, but no ecchymoses. The spleen was not palpable, and no other physical abnormality was noted. Blood examination showed haemoglobin 37 per cent. (5·18 gm. per 100 ml.), red cells 1·44 million per c.mm., colour index 1·28, white cells 3,000 per c.mm. (of these 1,400 were polymorphonuclear), reticulocytes 1·0 per cent., platelets 40,000 per c.mm., cell-volume 16·8 per cent., and mean corpuscular volume 115·1 c.μ. A histamine test meal showed free HCl in the gastric juice. The serum-bilirubin, erythrocyte fragility curve, X-rays of pelvis and femora, and faecal fat estimation were all normal. Sternal marrow biopsy revealed a hypoplastic marrow containing a great deal of fat and consisting mainly of red cells; only a few small islands of blood-forming cells were found. He was given four injections of 3 ml. 'anahaemin' intramuscularly, and although on one occasion the reticulocyte count rose to 3·0 per cent. there was no sustained haematological response. He then received two blood transfusions, and on discharge was free of symptoms, the haemoglobin being 73 per cent. (10·2 gm. per 100 ml.). He continued to attend for transfusions, at first weekly, receiving the packed cells of two pints of blood on each occasion. After five months he required the cells of only one pint each fortnight. There was little technical difficulty, but he became very depressed, and hated each transfusion more than the last. In March 1944 his blood count began to rise spontaneously, and since that date no further treatment has been required. He has since worked as a chauffeur, as a travelling salesman, as a fisherman, and as a miner, but when last seen on May 18, 1950, it was evident that he was suffering from thyrotoxicosis, and he is awaiting surgical treatment for this complaint. His blood count on this occasion showed haemoglobin 90 per cent. (12·6 gm. per 100 ml.), red cells 4·50 million per c.mm., colour index 1·0, white cells 5,600 per c.mm., reticulocytes 1·8 per cent., and platelets 240,000 per c.mm.

Comment. A case of chronic idiopathic aplastic anaemia, with complete recovery after transfusion over a period of nine months. Though technical difficulty was slight, the patient had several psychological upsets during his period of attendance for treatment, and it is interesting to speculate on the relation of this emotional disturbance to the development of the thyrotoxicosis from which he is now suffering.

Case 19. A typist, aged 19 years, was admitted to the Royal Victoria Infirmary under the care of Dr. A. G. Ogilvie on January 25, 1949. She was well until two months before admission, when she was noticed to be pale. The pallor increased, and she became tired, listless, and breathless, and had severe palpitations. She fainted on three occasions, and had frequent occipital headaches, which were made worse by stooping. On three occasions her nose had bled profusely. Her last menstrual period, three weeks before admission, had lasted 11 days, and the loss of blood was heavy. There was no history of any previous serious illness, and on careful questioning no history of drug-taking or of contact with any noxious substance was elicited. On examination she was severely anaemic; there was no purpura in the skin, nor was she bleeding, but there were small scattered haemorrhages in the optic fundi; the throat was clean, the spleen was not palpable, and no other physical signs of note were discovered. Blood examination showed haemoglobin 13 per cent. (1·8 gm. per 100 ml.), red cells 0·68 million per c.mm., colour index 0·96, white cells 2,300 per c.mm. (54 per cent. polymorphs), mean corpuscular volume 87 c.μ, reticulocytes 1·8 per cent., and platelets 35,000 per c.mm. Hess's capillary fragility test was positive. She was given a blood transfusion of the packed cells of four pints immediately on admission, and her condition improved. A histamine test meal showed free HCl in the gastric juice. The serum-bilirubin, erythrocyte fragility curve, and X-rays of both femora and of the pelvis showed no abnormality. Three specimens of marrow removed by sternal puncture showed an extremely hypoplastic marrow; the specimens consisted mainly of fat, and there was severe depression of blood formation. A surgical biopsy of the iliac crest confirmed these findings.

One week after admission she began to have severe epistaxis; the following day there was haemorrhage from the right external auditory meatus, she started to bleed heavily per vaginam, and frank purpura of the skin developed. From this point her progress was extremely stormy. Between February 2 and March 10 the cells of 31 pints of blood were given. The epistaxis and bleeding from the ear subsided, but the metrorrhagia continued unabated and, since the technical difficulties of transfusion were increasing daily, a gynaecological opinion was sought. Dilatation and curettage of the uterus was performed on March 10, and 25 millicuries of radium were inserted into the uterine cavity and left *in situ* for 72 hours. After the operation the uterine bleeding decreased, and the patient's general condition steadily improved. Her recovery was retarded by an acute urinary infection, which responded to treatment. Despite the diminution of the haemorrhage the patient's haemoglobin fell steadily, and two further transfusions were necessary. On her discharge on March 31 there was only slight uterine haemorrhage. A blood count showed haemoglobin 73 per cent. (10·2 gm. per 100 ml.), white cells 4,400 per c.mm., and reticulocytes 0·7 per cent. She remained bedridden at home, and uterine haemorrhage, though slight, was continuous. She was re-admitted fortnightly to be given transfusions by one of us (J. N. W.); the scarcity of accessible veins was at times an almost insurmountable problem. Her repeated attendance for transfusions produced considerable psychological trauma to both patient and doctor; the patient dreaded each

attendance more than the last, and we who had to treat her came to dread the technical difficulty of the procedure more each time, and on several occasions were on the point of giving up. But transfusion became progressively easier, and from July 1949 the patient received the packed cells of five pints every four weeks. She continued to have steady uterine bleeding, and on September 1, 1949, her medical attendant, Dr. R. M. S. Parker, gave her 5 mg. of stilboestrol every four hours. Within 24 hours all bleeding ceased, and the stilboestrol was reduced to 5 mg. every other day. For the first time in eight months she began to get up; further transfusions were required on September 7 and November 22, 1949, but thereafter she improved spontaneously. In October the dosage of stilboestrol was reduced to 5 mg. every four days, and in January 1950 it was withdrawn; to our surprise there was no oestrin-withdrawal bleeding. Since that time she has had normal menstrual periods. On April 14, 1950, her haemoglobin was 83 per cent. (12·2 gm. per 100 ml.); she had had no transfusion since November. A specimen of marrow removed from the iliac crest by puncture on April 14 was still hypoplastic, but on April 28 a sternal specimen showed an active normoblastic marrow. She has now recommenced work, and is in good health. When she was last seen on June 16, 1950, the blood count showed haemoglobin 80 per cent. (11·8 gm. per 100 ml.), red cells 4·36 million per c.mm., colour index 0·93, white cells 5,000 per c.mm., and reticulocytes 1·8 per cent.

Comment. A very severe case of acute idiopathic aplastic anaemia, with recovery. Treatment was continued over a period of nine months despite great technical and psychological difficulties. This case illustrates the value of persistent treatment even when the outlook appears hopeless. The recurrence of normal menstrual periods after radium, and the unusual response to stilboestrol are difficult to explain.

Case 16. A station-master, aged 63 years, was admitted to the Royal Victoria Infirmary under the care of one of us (T. H. B.) on August 26, 1948. He had been quite well until two months before admission, when he was noticed to be pale and became breathless on exertion. He was seen by a physician, who advised injections of liver extract, but three injections produced no improvement in his condition. One month before admission he had an attack of vomiting and diarrhoea. After three days in bed this complaint cleared up, but on getting out of bed he fainted, and during the next two weeks he became increasingly pale and breathless. There was no history of haemorrhage. He had not been exposed to any significant drug or toxic substance. On examination he was breathless at rest, and there was marked general pallor, but the optic fundi were normal. There were no purpuric spots or ecchymoses. There was no evidence of haemorrhage, the spleen was not palpable, and no other abnormal physical signs were noted. Blood examination showed haemoglobin 37 per cent. (5·2 gm. per 100 ml.), red cells 1·83 million per c.mm., colour index 1·01, white cells 2,900 per c.mm. (40 per cent. polymorphs), reticulocytes 1·2 per cent., mean corpuscular volume 90 c.μ, and platelets 50,000 per c.mm. A histamine test meal showed normal gastric acidity. The serum-bilirubin and erythrocyte fragility curve were normal, as were X-rays of the skull, pelvis, and right femur. A barium meal examination was normal, and there was no occult blood in the stools. Sternal puncture revealed an extremely fatty hypoplastic marrow. Of the nucleated cells 57 per cent. were lymphocytes; very few normoblasts and myelocytes were present. By September 15 the patient's haemoglobin had fallen to 27 per cent., and he was accordingly given a transfusion of the packed cells of three pints of blood. He then felt very much better, and was discharged. He attended

monthly for transfusions, receiving the packed cells of four pints of blood on each occasion, and between attendances led an active life. On December 9, 1948, he was given a transfusion into the sternum of 2 ml. of marrow from a donor of identical genotype in addition to blood transfusion, and this was repeated on two further occasions. In the early months of 1949 blood was required less frequently, and he received his final transfusion on July 19, 1949. On September 1, 1949, his haemoglobin was 82 per cent. (12·1 gm. per 100 ml.), and on February 23, 1950, with no further transfusion, it was 84 per cent. (12·3 gm. per 100 ml.). He has recently left the district, but insists on travelling almost 100 miles for regular blood counts and supervision, although he is evidently cured.

Comment. This case of chronic idiopathic aplastic anaemia shows that recovery can occur in the elderly as well as in the young. Transfusions of genotyped marrow were given, but it is difficult to assess their value; they did not replace blood transfusion as a therapeutic agent.

Several other cases call for brief individual comment.

Case 25. This patient, a boy of 15 years, suffering from acute idiopathic aplastic anaemia, has been under treatment for two years. In addition to repeated blood transfusions, he has had intrasternal injections of genotyped marrow on several occasions; the interval between his transfusions is becoming longer, and the psychological and technical difficulties, though great, are being surmounted. A recent biopsy shows a reacting marrow, and this boy can justifiably be regarded as on the road to recovery.

Case 8. A married woman of 44 years, suffering from chronic idiopathic aplastic anaemia, lived an active life for four of the five years during which she attended for transfusions. She had frequent hysterical outbursts, particularly if anyone apart from one of us (T. H. B.) attempted to give her transfusions. For the last year of her life she became partially bedridden and was constantly weak, tired, and lacking in energy. General pigmentation of the skin developed, and liver function tests suggested a considerable degree of hepatic insufficiency. Throughout the whole of her five years of treatment she received weekly transfusions, but never showed any sign of recovery, and eventually died at home of mesenteric thrombosis.

Case 9. This sufferer from chronic idiopathic aplastic anaemia was a married woman of 36 years, who managed to run a home and look after her five children while attending the hospital monthly for transfusions for a period of two years; she then had a typical incompatibility reaction following a transfusion, although the blood given was of her own group. Direct cross-matching showed no evidence of incompatibility, and to naked-eye inspection by one of us (T. H. B.) the blood appeared to be in perfect condition. The antigen concerned in the reaction was not discovered, but it seems possible that the blood was infected. The patient developed anuria and hyperpyrexia, and died within 24 hours. At *post mortem*, in addition to generalized skin pigmentation and haemosiderosis, there were pyaemic abscesses in the lungs and the typical pathological appearance of the 'transfusion kidney'.

Case 12. A clerk, aged 30 years, suffering from the chronic idiopathic variety of the disease, lived a normal life for two years between his monthly attendances for transfusion. He was then admitted to another hospital suffering from what was thought to be an abscess of the thigh; this was incised, and proved to be a haematoma, from which he subsequently bled to death.

Case 7. A married woman, aged 35 years, suffering from rheumatoid arthritis, had had several full courses of gold treatment, the last ending two years before the onset of her anaemia. For several months before admission she had taken 100 aspirin tablets weekly and, in addition, 'Eade's rheumatic pills', one three times daily. The latter contain colchicine gr. $\frac{1}{80}$ in each pill, and in view of the known action of colchicine in inhibiting mitosis it seems possible that this drug was the cause of her anaemia. Although severely disabled by her arthritis, she was able to do some housework and to look after her family in the intervals between her transfusions. After eight months' treatment she suddenly became comatose after a transfusion and died; autopsy showed that death had been due to a massive cerebellar haemorrhage.

Prognosis

Of the 25 cases of aplastic anaemia reviewed six patients have recovered completely, one appears to be recovering, and four others lived active lives for periods varying from eight months to four years after their first admission to hospital. It appears that with the improved modern technique of blood transfusion the prognosis of this condition is by no means hopeless. Every case of aplastic anaemia has a chance of recovery, and while the chance is undoubtedly greater in the cases due to toxic substances, the fact that recovery can occur in the acute idiopathic variety is exemplified by Case 19 of the present series.

Recommendations for Treatment

1. *Technical.* The technique of transfusion has varied from case to case in this series, and indeed many different methods have been used in the same patient, for with the passage of time difficulties may multiply owing to inevitable venous thrombosis. Whenever possible a No. 1 needle or an ordinary transfusion needle has been inserted into a vein by venepuncture, whether the vein was a small one on the dorsum of the hand or foot, a large antecubital vein, the external jugular, or the femoral. In some difficult cases the method of using a 20 ml. syringe and three-way tap, with a No. 12 needle, has been used; this technique undoubtedly produces the least trauma to veins, although it is the most time-consuming. Veins have been cut down upon as little as possible, but where this has been necessary a Bateman cannula (the inner or outer cannula, whichever was possible) or a polythene catheter has been inserted into a superficial vein in one of the extremities. The use of the polythene catheter as described by Farquhar and Lewis (1948) is particularly recommended in the restless, nervous patient, since the limb into which the blood is being given can be moved about with comparative safety. When large veins remain patent the method described by Walker (1948), in which polythene tubing is passed into a vein through a transfusion needle, and the latter is then removed, is valuable. Venous spasm, which may prove a frequent obstacle to the use of the Bateman cannula, particularly in small veins, appears much less troublesome when a length of polythene tubing is fed into the vein. Even when the greatest care is taken with transfusions there may be, particularly in the acute cases, a critical period some four or five months after beginning transfusions when the shortage

of veins becomes acute. Persistence beyond this point will in a number of cases lead to eventual recovery. The conservation of veins is of the utmost importance, and we feel therefore that the treatment of patients with aplastic anaemia should be undertaken by a member of the medical staff who has considerable experience in transfusion technique.

2. *Psychological.* Once the long and trying régime of repeated transfusions has begun, there is no doubt that the procedure may become increasingly arduous to both patient and doctor, and psychological upsets are common in these patients. They come to dread their repeated attendance, and even though they realize that their only hope of recovery lies in frequent transfusions, they may occasionally require considerable persuasion to return to hospital. They also tend to become accustomed to one doctor and to rely upon him, and emotional outbursts are common if a new member of the medical staff proposes to carry out a transfusion. It is thus evident that they require sympathetic and careful management, and it is desirable that, as far as possible, one individual should undertake the continued treatment of each patient.

3. *Nursing.* Careful nursing supervision is essential; there can be few experiences more heartbreaking than to find that, after a transfusion has been erected with considerable difficulty, it has been allowed to stop prematurely. A 'drip' transfusion if left unattended will stop spontaneously (Walton, 1947), and it is important that whenever possible each patient should receive individual attention from a special nurse.

4. *Selection of cases.* It is evident from the difficulties outlined above that careful selection of cases for treatment is essential. There are some patients, particularly the elderly and obese, and those suffering from a complicating disease of poor prognosis such as, for example, severe hypertension, in whom the technical difficulty of transfusion and the trauma which would be produced by frequent admission to hospital make it unjustifiable ever to begin treatment. Psychological factors are also of great importance in this context in view of the co-operation required of the patient, and while they should never be the sole reason for refusing to institute the 'transfusion life', it is certain that in some cases, when added to physical contra-indications, they will tip the scales against treatment. Wherever treatment has any chance of succeeding it should be pursued vigorously.

5. *Complications.* In the present series *transfusion reactions* have been a common complication. In the early cases cross-matching of blood was invariably done in the ward by the direct method, but in recent years a specimen of the patient's serum has been sent for matching at the Regional Transfusion Laboratory. In these cases the tube technique with saline and albumin has been used, and the indirect Coombs test has been done as a routine, as well as tests for zoning antibodies. The effect has been to reduce noticeably the number of untoward reactions to transfusion, and the tests are of particular importance in view of recent reports of multiple antibody reactions after repeated transfusions (Collins, Sanger, Allen, and Race, 1950; Malone and Cowen, 1950). *Cardiac failure* following transfusion can be avoided by giving only small transfusions

of packed cells (100 to 250 ml.) very slowly, if the patient's initial haemoglobin level is low. At a later stage in treatment it is usually possible to give the cells of three, four, and even five pints in a single transfusion with impunity, provided each pint is given in not less than four hours. *Persistent haemorrhage* is often the most difficult feature to control, and it may be that the new adsorbable haemostatics will prove to be of value in this field. Epistaxis, retinal haemorrhage, purpura, and bleeding from the gums frequently resolve after adequate transfusion, and it is perhaps surprising that we have found fresh blood to be no more efficient than banked blood in such circumstances. Uterine haemorrhage in particular may prove intractable, and at times is an almost insuperable problem. Surgical intervention is often necessary; hysterectomy is the most efficient method of controlling severe bleeding, but naturally this step could only be taken as the last resort in a young patient. Dilatation and curettage of the uterus and radium implantation are less efficient, but can reasonably be tried when the haemorrhage is moderate but persistent. Stilboestrol proved effective in Case 19 of the present series, but it is difficult to explain why no oestrin-withdrawal bleeding took place when it was stopped. The routine use of antibiotics has reduced the danger from the *infective conditions* to which such patients are extremely susceptible owing to their granulocytopenia. Thrombophlebitis in particular can often be aborted by adequate penicillin therapy. Embolic phenomena are exceedingly rare from the *phlebothrombosis* which may follow blood transfusion, but if the thrombosis shows signs of spreading, the anticoagulant remedies are now available for its control. *Air embolism* as a complication of treatment has not been observed in the present series, and should never occur if transfusions are carefully supervised. Certain other catastrophes, such as intracranial haemorrhage, are obviously unavoidable, but it is clear that if due precautions are taken, and if modern techniques and remedies are utilized to the full, the complications in treatment of patients with aplastic anaemia will in time to come be much less numerous than in the past.

Conclusion. The treatment of patients with aplastic anaemia is arduous, time-consuming, and fraught with difficulties, but it is our view that if it is diligently and sympathetically pursued an increasing proportion of recoveries from this disease will be reported in the future.

Acknowledgements

Our thanks are due to the physicians of the Royal Victoria Infirmary for permission to consult their records and to refer to patients who have been under their care. We are also indebted to the numerous members of the medical and nursing staff who assisted in the treatment of the patients in this series, to Professor F. J. Nattrass and Dr. R. B. Thompson for valuable criticism, and to Miss E. Blackburn and Mr. J. Andrews for help with the manuscript and figures.

Summary

Twenty-five cases of aplastic or 'refractory' anaemia are reviewed. Seven were symptomatic, the remainder idiopathic.

The age- and sex-incidence, symptoms, and clinical and pathological picture in these cases are briefly reported. The disease is equally common in the two sexes and can occur at any age, although it appears to be rare in early childhood. In 16 cases the peripheral blood picture was macrocytic, in the other nine normocytic; the sternal marrow was hyperplastic in five cases, hypoplastic in nine, and completely aplastic in nine.

Repeated blood transfusion is the only effective treatment, though intrasternal injection of genotyped marrow may have some adjuvant value.

Six patients (three with the symptomatic and three with the idiopathic disease) have recovered completely, and one further idiopathic sufferer appears to be recovering. Four other patients died after living reasonably active lives for periods of from eight months to four years.

The majority of patients with aplastic anaemia should be regarded as capable of recovery, and transfusion should be pursued energetically, except in the small group of elderly individuals in whom it is unjustifiable to begin treatment at all. Surgical intervention may occasionally be necessary to stanch haemorrhage.

Technical and psychological factors make it important that an experienced person should undertake the continued treatment of patients with this disease.

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SUBACUTE BACTERIAL ENDOCARDITIS[1]

A review of 442 patients treated in 14 centres appointed by the Penicillin Trials Committee of the Medical Research Council

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In February 1945 the Penicillin Trials Committee of the Medical Research Council appointed 14 centres in Great Britain to study the value of penicillin in subacute bacterial endocarditis, and by January 1949 442 patients had been treated under this scheme. The main results have already been published (Christie, 1946, 1948, 1949), and several teams have described various details of their findings (Ward, Meanock, Selbie, and Simon, 1946; Smyth and Wilson, 1946; MacIlwaine, 1947; Jones, Herring, Langley, and Oleesky, 1947; Bramwell, 1948; Matthew and Gilchrist, 1948–9; Selbie, Simon, and Robinson, 1949; Porterfield, 1950; Matthew, 1950). The purpose of the present paper is to analyse in greater detail the records of patients treated under the M.R.C. scheme, for they provide a unique opportunity to study not only the effect of penicillin, but the influences of age, sex, various underlying heart lesions, and other factors in subacute bacterial endocarditis.

Material

The numbers of patients treated in each centre are shown in Table I. The centres agreed to adopt different systems of treatment, some of which are now known to be inadequate, so that it would be misleading and invidious to compare their results.

Selection. When the trials began only patients with positive blood cultures were accepted, because the diagnosis in those with negative cultures might have been open to question. But most centres encountered a few patients who, in spite of persistently negative cultures, showed all the other signs of the disease. Some were given penicillin, and reports of 34 were collected later. These cases are reviewed separately in the last section. Most of this paper deals with 408 cases in which positive blood cultures were obtained before treatment began. Patients with acute bacterial endocarditis have not been included, but those who pursued a clinical course that was subacute, although infected with a virulent organism, have been included. Strictly speaking, endocarditis does not include infections confined to a patent ductus arteriosus or an aortic coarctation, but these cases too have been included. Most patients were sent to one

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of the centres without first being given penicillin, but 21 had received a short course (of 10 days or less), and 29 had received a longer course, before being transferred to a centre. These courses of treatment have not been included in the M.R.C. trials, but patients so treated were used, along with those who relapsed under the M.R.C. scheme, to assess the effect of penicillin in relapsing

TABLE I

Numbers of Cases Treated in the Different Centres

Centre	*With positive blood cultures*	*With negative blood cultures*
Belfast	22	6
Birmingham	67	6
Bristol	28	..
Cardiff	13	..
Edinburgh	27	7
Glasgow	32	3
Leeds	26	..
Liverpool	20	..
Manchester	57	7
Newcastle	12	..
Sheffield	11	..
London — St. Mary's	22	..
London — Middlesex	24	..
London — St. Bartholomew's	47	5
	408	34

Records of cases with negative cultures from eight centres were not available.

infections. Apart from the above considerations there was no deliberate selection of cases; no patient was refused treatment because he was too ill, or because the infecting organism was resistant to penicillin. However, 677 deaths in England and Wales were certified as due to bacterial endocarditis in 1945, while between February 1945 and March 1946 only 269 patients were treated under the M.R.C. scheme; the age- and sex-distribution, and other features, of the M.R.C. series may therefore not exactly represent 'the whole population' of subacute bacterial endocarditis in this country. For this reason the annual reports of the Registrar General have also been analysed.

Follow-up. 269 patients were treated between February 1945 and March 1946, and another 139 were treated between March 1946 and December 1948. The last follow-up reports were received early in 1949, so that the period of surveillance ranged from over four years for those treated in 1945 to a few months for those treated in 1948. During this period nine patients were 'lost', at intervals between three months and two years after their apparent cure (Table XII, column 3). One centre omitted to follow for more than a few months five other cases of apparent cure. One patient was killed in an accident. All these patients are treated as having been 'cured' at the date on which they were last known to be well. Although the follow-up period varied from a few months to over four years, most patients who died did so within six months of treatment (Fig. 3). Therefore differences in the length of follow-up do not introduce a serious discrepancy. Only five cases were followed for less than six months.

Incidence

The M.R.C. series did not reveal the incidence of bacterial endocarditis in the general population. However, for many years figures have been provided by the Registrar General, and although these have been analysed before (Perry, 1936) they have received little attention recently. Since 1931 the Registrar General has published deaths in England and Wales certified as due to 'acute or subacute bacterial endocarditis'. Before that year these diseases were included under a wider heading of 'malignant endocarditis', which consisted of bacterial endocarditis (about 90 per cent.) and endocarditis not specified as bacterial (about 10 per cent.). From 1911 to 1918 there were 4,581 deaths from malignant endocarditis, an average of 573 a year; the crude death-rate varied between 11 and 18 per 100,000, and differed little between male and female subjects. In 1919 deaths began to rise, and in 1921 reached a peak of 1,203, which included 724 male patients. Possible reasons for the increased incidence of the disease among men after the war were widely discussed at the time. By 1924 deaths from malignant endocarditis settled to a steady rate of about 1,000 a year, male and female subjects being affected equally. In the 14 years from 1931, when deaths were more precisely shown as due to 'acute or subacute bacterial endocarditis', to 1944, after which penicillin began to be used, there were 13,495 deaths, an average of 964 a year; again the numbers of male and female patients were almost equal (6,668 male and 6,827 female). The accuracy of these statistics is set by that of death certificates, and any error there may be is likely to be one of underestimation, for patients suspected of the disease are often sent to hospital, where the diagnosis can be established, while others with the disease may die at home without the diagnosis being suspected.

Age incidence. In the M.R.C. series the disease was rare under the age of 15 years; after that the incidence mounted steeply, and reached its maximum between the ages of 20 and 25 years; patients between 15 and 35 years old formed 62 per cent. of the total (Fig. 1). The age incidence in all forms of bacterial endocarditis has its peak at a slightly later age, as shown by the Registrar General's figures superimposed on Fig. 1; this is because acute infections by organisms other than *Streptococcus viridans* fall more heavily on older patients (Anderson and Keefer, 1948).

Sex incidence. In the M.R.C. series the sexes were affected almost equally: there were 202 male and 206 female patients. As mentioned above, between 1924 and 1944 the Registrar General's reports showed an equal incidence in the two sexes. But after the first world war, and again from 1945 to 1948, the certified deaths showed more men than women, the ratio being three to two. This suggests that the M.R.C. series, in which the sexes were equally distributed, was not representative. But the death-rate since 1945 no longer reflects the attack rate, and there is some evidence from the M.R.C. series that penicillin, in the doses then used, was more effective in women than in men, irrespective of their ages. Furthermore, the M.R.C. series contained only subacute infections, while the Registrar General's figures include acute bacterial endocarditis, which

seems to be commoner in men. The difference in incidence is shown in the American series (Anderson and Keefer, 1948), in which infections with 'non-haemolytic streptococci' affected the sexes almost equally (235 male and 221 female patients) though with other infections, due mostly to virulent organisms, 142 out of 230 patients (62 per cent.) were male. It therefore seems that subacute bacterial endocarditis affects the two sexes almost equally. But the sex incidence

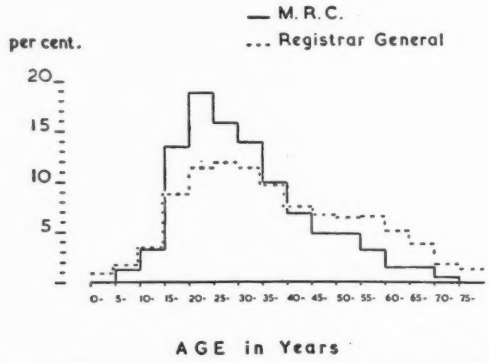

FIG. 1. The age incidence in 408 cases in the M.R.C. series, compared with the age incidence in 4,531 deaths due to acute or subacute bacterial endocarditis derived from the Registrar General's Reviews 1940–4. Ages are shown in groups of five years.

differs significantly in young and old patients. Below the age of 35 years 59 per cent. of patients in the M.R.C. series were female; over that age 61 per cent. were male. It will be seen later that part of the reason for this difference is that infection of the mitral valve is far more common in young women. The same distribution is found in all forms of bacterial endocarditis; in the Registrar General's figures from 1940 to 1944, 56·8 per cent. of patients below 35 years old were women and 55·2 per cent. above that age were men.

Underlying Heart Disease

The sites of underlying heart disease are set out in Tables II and III. Since the diagnosis in all patients who recovered, and in all who died without autopsy, was made on clinical grounds, it is important to assess its accuracy. There were macroscopic post-mortem findings in 89 patients, and, with the exception of tricuspid involvement, the clinical diagnosis of the sites of valvular disease was correct in 79; in seven patients other valves were found to be affected (possibly owing to spread of the disease after the original diagnosis had been made), and in three patients valves thought to be diseased were found to be healthy. From these findings errors in clinical diagnosis of the site of the lesion seem to be small. Whether the affected valve was incompetent or stenotic was not often specified. Moreover, as Kelson and White (1945) showed, the clinical diagnosis,

TABLE II

The Distribution of Age, Sex, and Underlying Lesions in the Whole Series of 408 Patients, and in the 195 Fatal Cases

Nature of underlying lesion / Sex		Whole series														Fatal cases													
		Acquired						Congenital		Both acquired and congenital		Bicuspid aortic	Total			Acquired						Congenital		Both acquired and congenital	Bicuspid aortic	Total			
		Mitral		Aortic		Mitral and aortic										Mitral		Aortic		Mitral and aortic									
		M	F	M	F	M	F	M	F	M	F	M	M	F	Total	M	F	M	F	M	F	M	F	M	M	M	F	Total
Ages (in five-year groups)	5–	..	1	..	..	..	..	2	2	..	..	..	2	3	5	..	1	..	..	..	..	..	1	..	..	..	2	2
	10–	..	2	..	..	1	2	3	5	..	..	..	4	9	13	..	..	..	..	..	..	..	3	..	..	..	3	3
	15–	8	20	2	..	10	8	3	3	..	..	1*	24	31	55	5	6	..	..	4	2	2	1	..	1*	12	9	21
	20–	7	26	5	2	15	13	4	5	..	..	..	31	46	77	5	10	4	..	9	5	..	1	..	..	18	16	34
	25–	7	17	6	..	15	13	3	2	1	..	1	33	32	65	1	7	2	..	7	8	1	..	..	1	12	15	27
	30–	6	14	3	1	12	16	1	..	..	1	3*	25	32	57	3	6	..	..	8	8	..	..	..	3*	14	14	28
	35–	9	8	6	1	10	4	1	1	..	..	1	27	14	41	3	3	3	1	8	2	..	..	..	1	15	6	21
	40–	4	7	8	1	4	1	1	1	..	..	1	18	10	28	2	3	4	1	3	1	..	..	..	1	10	5	15
	45–	5	3	2	1	3	2	3	1	..	..	..	13	7	20	1	1	2	1	2	2	1	..	..	..	6	4	10
	50–	6	3	..	..	2	7	..	1	1	..	..	9	11	20	4	1	..	..	2	6	..	..	1	..	7	7	14
	55–	5	2	..	2	3	1	..	..	..	..	..	8	5	13	2	1	..	2	3	1	..	..	..	..	5	4	9
	60–	3	2	1	..	..	..	..	..	..	..	..	4	2	6	3	1	1	..	..	..	..	..	..	..	4	1	5
	65–	..	3	2	..	1	..	..	..	..	..	..	3	3	6	..	2	1	..	1	..	..	..	..	..	2	2	4
	70–	..	1	1	..	..	..	..	..	..	..	..	1	1	2	..	1	1	..	..	..	..	..	..	..	1	1	2
Total		60	109	36	8	76	67	21	21	2	1	7	202	206	408	29	43	18	5	47	35	4	6	1	7	106	89	195

* Mitral valve also involved in one case.

particularly of stenosis of the mitral valves, is often wrong. This view is supported by post-mortem findings in the M.R.C. series. Thus the clinical diagnosis that the mitral valve alone was affected was confirmed at autopsy in 29 cases; but the pathologist reported actual stenosis of the valve in only two of these, although it had been thought to be present in nine; similarly, of 45 patients with both aortic and mitral disease mitral stenosis was diagnosed in 12, and

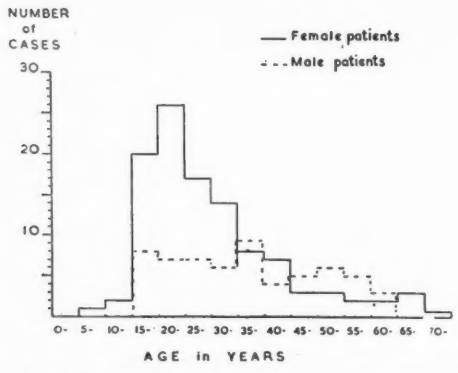

FIG. 2. Mitral disease in the two sexes. It was more common in female than male patients, particularly in young women. Ages are shown in groups of five years.

reported at *post mortem* in six. It would therefore be meaningless to present the various valve deformities diagnosed, and only the sites of underlying lesions have been considered.

Mitral disease. In 169 cases (41 per cent. of the whole series, and 46 per cent. of patients with acquired lesions) there was evidence of disease of the mitral valve alone. It affected almost twice as many female as male patients (109 and 60). Of the female patients 70 per cent. were between the ages of 15 and 35 years, but in men the disease fell fairly evenly on all age-groups over 15 years (Fig. 2).

Aortic disease. The aortic valves alone were affected in 44 cases, excluding those in which the valve was found to be bicuspid. Of these patients 36 were male and eight female; 75 per cent. were between the ages of 20 and 45 years. If bicuspid lesions found *post mortem* are included, the preponderance of males becomes even more remarkable, for the seven who had such lesions were all male patients, and in five the disease was confined to the aortic valves, so that of 49 patients with disease of the aortic valve alone 41 (83 per cent.) were male.

Mitral and aortic disease. Both valves were diseased in 143 cases; it was obviously not possible to say during life whether bacterial infection was confined to one valve or affected both. The sexes were affected almost equally (76 male and 67 female patients), and 116 were between 15 and 40 years of age.

All told, the mitral and aortic valves were affected alone or together in 363 patients, including seven with bicuspid aortic valves; of these there was mitral disease in 314, or 86 per cent. (alone in 169, combined with aortic disease in 143, and with a bicuspid aortic valve in two); there was aortic disease in 192, or 53

per cent. (alone in 49, including five with bicuspid valves, and combined with mitral disease in 143).

Tricuspid disease. Disease of the tricuspid valve was not diagnosed during life in any patient. Of the 89 post-mortem examinations vegetations, or healed vegetations, were reported in four; in all these cases there was deformity or disease of both aortic and mitral valves.

Congenital heart disease. There were 45 patients with congenital heart disease, including three in whom rheumatic heart disease was also present. The lesions

TABLE III

The Distribution of Age, Sex, and Nature of Underlying Defect in 42 Patients with Congenital Heart Disease and Three with both Congenital and Rheumatic Heart Disease

		All cases; underlying defect													*Fatal cases*		
		Ventricular septal defect		*Pulmonary stenosis*	*Fallot's tetralogy*	*Atrial septal defect*	*Ductus arteriosus*		*Coarctation*	*Unspecified congenital*		*Total*			*Total*		
Sex		*M*	*F*	*M*	*F*	*M*	*M*	*F*	*M*	*M*	*F*	*M*	*F*	*Total*	*M*	*F*	*Total*
Age (in five-year groups)	5–	1	..	1	..	..	..	1	..	..	1	2	2	4	..	1	1
	10–	..	2	1	1	..	1	2	..	1	..	3	5	8	..	3	3
	15–	3	1	..	1	..	..	1	..	..	..	3	3	6	2	1	3
	20–	4*	3	..	..	..	..	2	..	..	..	4	5	9	..	1	1
	25–	3§	1	..	..	..	..	1	..	1‡	..	4	2	6	1	..	1
	30–	1	..	..	..	..	..	1†	..	..	..	1	1	2	..	..	..
	35–	..	1	..	..	..	1	..	..	..	..	1	1	2	..	..	..
	40–	..	..	..	..	..	..	1	..	1	..	1	1	2	..	..	..
	45–	1	..	..	..	1	..	..	1	..	1	3	1	4	1	..	1
	50–	1‖	..	..	..	..	..	..	..	..	1	1	1	2	1	..	1
Total		14	8	2	2	1	2	9	1	3	3	23	22	45	5	6	11

* One case with pulmonary stenosis.
† With mitral stenosis.
‡ With an unspecified rheumatic lesion.
§ One case with dextrocardia.
‖ With rheumatic aortic incompetence.

are set out in Table III. The sex incidence in this group was equal, but a ventricular septal defect was slightly commoner in male patients, while of 11 with a ductus arteriosus nine were female. Ages ranged from seven to 52 years, though 27 patients (60 per cent.) were under 25, including 12 under 15 years old. In children under 15 years congenital were twice as common as acquired lesions. There were two unusual cases: a man with an infected coarctation, and a man with an infected atrial septal defect; both patients died at home, and there was no autopsy.

Bicuspid aortic valves. Seven patients were found at *post mortem* to have this lesion. They are shown separately in Table II. To distinguish congenital from acquired bicuspid aortic disease demands special methods (Lewis and Grant, 1923) and in the present series there is insufficient pathological evidence to do so.

Aetiology of the underlying lesion. To distinguish clinically between congenital and acquired lesions presents difficulty only in bicuspid aortic disease. But to

tell in each case of acquired disease whether there has been previous rheumatic, arteriosclerotic, or syphilitic disease, or whether the valves were previously normal, is often difficult or impossible. In the first 269 cases there were 243 with lesions which were not congenital, but specific information about aetiology was not sought. In the second series of 139 cases, in all of which the aetiology of the lesion was specifically sought, there were 120 with acquired lesions. Of these the aetiology was rheumatic in 91 (76 per cent.), there was no history of rheumatic

TABLE IV

Evidence of Antecedent Rheumatic Heart Disease at Autopsy in 86 Patients with Acquired Heart Disease

Primary cardiac lesion	*History of rheumatic fever or previous rheumatic heart disease*	*Number of cases*	*Macroscopic evidence of rheumatic heart disease*			
			None	*Slight or dubious*	*Definite*	*Not stated*
Mitral	Yes	13	..	3	9	1
	No	5	..	..	5	..
	Not stated	10	..	..	8	2
Aortic	Yes	7	2*‡	..	4	1
	No	4	..	2	1*	1*
	Not stated	1	1†	..	..	..
Mitral and aortic	Yes	30	..	8	15	7
	No	6	1*	3	2	..
	Not stated	5	..	2	2	1*
Mitral, aortic, and tricuspid	Yes	3	..	1	2	..
	No	..	..	..	..	..
	Not stated	1	..	1	..	..
No valve affected§	Not stated	1	..	..	1	..
Totals	Yes	53	2	12	30	9
	No	15	1	5	8	1
	Not stated	18	1	3	11	3
		86	4	20	49	13

* Bicuspid aortic valve.
† 'Probably congenital'.
‡ Imperfectly fused aortic valves.
§ Edges of mitral valve healthy; vegetation on MacCallum's patch extending on to the base of the valve.

fever and no known rheumatic heart disease in 13 (9 per cent.), and in the remaining 16 cases the aetiology was not specified. The macroscopic post-mortem findings set out in Table IV show that there were definite changes indicating underlying rheumatic heart disease in 49 of 86 patients with acquired heart disease. (By 'definite' is meant either a statement to that effect by the pathologist, or the description of a MacCallum's patch, or of thickening and scarring of a mitral valve with thickened and shortened chordae tendineae, except when these changes were due to healing or healed vegetations; lesser changes are classed as 'slight or dubious'.) In 20 of the 86 cases the changes were slight or dubious. In 13 the state of the valves was not specified, but in nine of these the aetiology had been classed as rheumatic by clinicians before autopsy. In only four cases was it stated that there was no evidence of rheuma-

tic heart disease at autopsy; bicuspid aortic valves were certainly present in two of these, and probably present in the other two. Although macroscopic appearances and clinical history cannot be used as an absolute proof of previous rheumatic infection, they are good evidence; it therefore seems that at least 90 per cent. of acquired lesions were probably rheumatic. In most of these cases the myocardium was not studied histologically, though work from Belfast and Edinburgh (MacIlwaine, 1947; Matthew and Gilchrist, 1948–9) showed that rheumatic changes were common. At autopsy, calcification of valves was seen in 14 of 86 cases with acquired lesions; it was limited to the aortic valves in five and to the mitral in five, and affected both valves in four cases; it was described as gross in four of the aortic and in one of the mitral lesions. It could not be ascertained in which cases this calcification was due to the healing of vegetations, and in which it was a sequel to rheumatic heart disease akin to that described by Karsner and Koletsky (1947). It was not arteriosclerotic in origin, for of the 14 cases there was macroscopic evidence of rheumatic heart disease in 10, and clinical evidence in three others. In fact, hypertensive and arteriosclerotic heart disease, cited as the underlying lesion in 2 per cent. of the American cases (Anderson and Keefer, 1948), was diagnosed in life only once in the M.R.C. series. Syphilis was apparently the sole cause of the underlying heart disease in one patient, a man of 74 years with an aortic aneurysm and a positive Wassermann reaction who died at home, and on whom there was no autopsy. A second patient had both syphilis and rheumatic heart disease, and in two other cases evidence of syphilis was merely a coincidental finding. Myocardial infarction was not the predisposing cause of bacterial endocarditis in any case, although in 10 patients autopsy showed myocardial infarction from emboli detached from vegetations. In no case was it certain that infection began in a heart which was previously normal. In two patients the heart at first appeared clinically to be normal; later both developed aortic lesions. One was found at autopsy to have a bicuspid aortic valve, and in the other, who survived, the same lesion is suspected. One patient at post-mortem had normal valves, infection having apparently originated on a MacCallum's patch and spread to the base of the mitral valve.

Infecting Organism

The infecting organism was identified as *Streptococcus viridans* in 87 per cent., and as a non-haemolytic streptococcus in another 7 per cent., of the M.R.C. patients. In the remainder other streptococci, staphylococci, *Haemophilus influenzae* or *para-influenzae*, and a pneumococcus were found, and in three there was a mixed infection (Table V). This distribution supports the assertion of Libman and Friedberg (1941)—a view generally held ever since Horder's work (1908–9)—that 'in over 90 per cent. of cases the causative organisms are non-haemolytic streptococci, usually of the alpha (viridans) and occasionally of the gamma (anhaemolyticus) variety'.

Definitions. The term *Streptococcus viridans* has been used in the M.R.C. series not as a description of a definite species, but to cover all the

α-haemolytic streptococci. When the trials began it was not generally appreciated how easily enterococci may be mistaken for organisms properly belonging to the *viridans* group, and it now seems likely that a few mistakes were made, for when Selbie, Simon, and Robinson (1949) and Porterfield (1950) re-examined many of the strains they found that four out of 119 organisms originally called *Streptococcus viridans* had the properties of enterococci. But these re-examina-

TABLE V

The Initial Infecting Organism in 408 Cases of Subacute Bacterial Endocarditis

The resistance to penicillin is expressed as a multiple of the resistance of the standard Oxford staphylococcus.

	Number of cases	*Coefficient of resistance*									
		¼ or less	*¼ to 1*	*–2*	*3–6*	*8–10*	*16–64*	*–300*	*'Resistant'*	*Unknown*	*Number 'cured'*
Streptococcus viridans	354	79	111	74	33	6	4	2	..	45	187
Non-haemolytic streptococcus	31	5	6	11	2	..	1	..	..	6	15
Micro-aerophilic *Strep. viridans*	1	..	1	..	..	..	..	..	..	..	1
Micro-aerophilic non-haem. strep.	5	2	1	1	..	..	..	..	..	1	2
Enterococcus	2	..	..	..	..	..	2	..	..	..	1
'Streptococcus'	1	..	..	..	..	..	..	1	..	..	..
Staphylococcus albus	4	..	2	1	1	..	..	..	..	..	1
Staphylococcus aureus	1	..	1	..	..	..	..	..	..	..	1
'Staphylococcus'	1	..	..	..	..	..	..	..	..	1	..
Pneumococcus	1	..	..	..	..	..	..	..	..	1	1
Haemophilus influenzae	3		1	..	..	..	..	..	1	1	1
Mixed infections:											
Strep. viridans and non-haem. strep.	1	..	..	1	..	..	..	..	..	..	..
Strep. viridans and pneumococcus	1	..	1	..	..	..	..	..	..	..	1
Staph. albus *Bact. faecalis alk.* Micrococci	1	..	..	..	..	..	..	..	..	1	1
Uncertain (culture died)	1	..	..	..	..	..	..	..	..	1	1
	408	86	124	88	36	6	7	3	1	57	213

tions were made on subcultures stored for years, and it is not certain that these subcultures were always the same as the original strains; it is even possible that the properties of *viridans* streptococci can change on culture (Clapper and Heatherman, 1950). For these reasons the classifications given in Table V are those of the original findings. Four of the strains of *Staphylococcus albus* were coagulase-negative; this test was not made on the other staphylococci. Whether the three organisms called *Haemophilus influenzae* were in fact *H. para-influenzae* was not determined.

Sensitivity to penicillin. Resistance to penicillin was measured in 351 organisms (Table V). The results are expressed as multiples of the resistance of the standard Oxford staphylococcus. Of 354 strains of *Streptococcus viridans*, penicillin-sensitivity was measured in 309, and these strains ranged from 20

times more sensitive to 300 times more resistant than the Oxford staphylococcus. But these extremes were rare, and 85 per cent. were between one-quarter and twice as resistant; only 4 per cent. were eight or more times as resistant as the standard Oxford staphylococcus. Only one of the 10 strains which were 16 times, or over 16 times, more resistant belonged to those later classed as enterococci by Selbie, Simon, and Robinson (1949) and Porterfield (1950). The

TABLE VI

Organisms in Reinfections or Delayed Relapses

The table includes all patients who became infected by a second organism, and patients who had a second attack (or relapse) after from eight months to over five years of apparent cure.

Duration of apparent cure	*Original organism*	*Second organism*	*Comment*
Nil	*Strep. viridans*	*Bact. coli*	From pyelonephritis
Nil	,,	*Ps. pyocyanea*	Occurred during penicillin therapy
161 days	,,	*Strep. faecalis*	From buttock infection
250 days	,,	*Strep. viridans*	Organisms not compared
11 months	,,	Non-haemolytic strep.	
13 months	,,	*Strep. viridans*	,, ,, ,,
17 months	Non-haemolytic strep.	Non-haemolytic strep.	,, ,, ,,
23 months	*Strep. viridans*	*Staph. albus*	
23 months	,,	*Strep. viridans*	Cultural differences
27 months	,,	,,	Second attack followed dental extraction
27 months	,,	Not known	
29 months	,,	*Strep. viridans*	Same penicillin sensitivity
31 months	,,	,,	Not compared
40 months	,,	,,	,, ,,
*50 months	,,	β-haemolytic strep.	
*59 months	,,	*Staph. albus*	
*64 months	,,	*Strep. viridans*	,, ,,

* These reinfections occurred after January 1949.

range of penicillin-sensitivity in 25 non-haemolytic streptococci was of the same order as that of the α-haemolytic streptococci.

Acquired resistance. In the M.R.C. series 65 patients with *Streptococcus viridans* infection relapsed, and an increase in resistance to penicillin was reported in 15; this increase was threefold or less in seven cases, between four- and tenfold in seven, and one hundred and sixtyfold in one. In this last case there were other reasons for suspecting that the second organism was different from the first. In five cases the organism became more sensitive to penicillin, and in two it developed some resistance which was later lost. Thus *Streptococcus viridans* does not often acquire resistance to penicillin, and when it does the increase is small. No change in resistance was reported in organisms other than *Streptococcus viridans.*

Mixed infections. A double infection was found in two patients; in a third, three different organisms were grown from the blood on different occasions, but there is some doubt whether all three organisms came from the heart.

MacLean and Howell (1947) showed that double infection, with two strains of the same species differing in penicillin sensitivity, may sometimes explain why there appears to be a great increase in penicillin resistance after unsuccessful treatment. This may be the explanation in the only case in the M.R.C. series in which resistance markedly increased.

Reinfections. It is not possible to ascertain whether a second attack of bacterial endocarditis is a relapse or a reinfection unless the second organism differs from the first. In three cases in the M.R.C. series blood cultures before treatment grew *Streptococcus viridans* alone, but another organism appeared later and killed the patient; the second organisms were *Ps. pyocyanea*, *Streptococcus faecalis*, and *Bact. coli* respectively. Two of these patients had been given penicillin by intramuscular infusion, which is known to lead to abscesses infected by penicillin-resistant organisms (Morgan, Christie, and Roxburgh, 1944) and in one of these patients the same organism (*Streptococcus faecalis*) was grown from such an abscess. *Bact. coli* pyelonephritis was present in the third case. Fourteen other patients had a second attack after being apparently cured for between eight months and five and a half years (Table VI). In three cases the second organism was clearly different from the first; in four cases there was clinical or bacteriological evidence that a new infection might have caused the second attack; in the remaining seven the first and second organisms were similar, but their cultural characteristics were not closely compared.

Foci of Infection

A focus of infection was sought in a representative group of 215 cases. This group consisted of patients treated after March 1946, and of those from three centres from the beginning of the trials. No focus of infection was found in 82 patients (38 per cent.); in 103 (48 per cent.) there were signs of dental sepsis or a history of tooth extraction, and in 30 (14 per cent.) some other focus was found (Table VII). Teeth had been removed less than three months before the onset of symptoms in 23 cases (10·7 per cent.), but in another eight cases (3·7 per cent.) teeth were removed after the onset of symptoms. This lends some support to the suggestion of Feldman and Trace (1938) that dental extraction may have no causal relation to bacterial endocarditis, and that teeth are removed to relieve symptoms of bacterial endocarditis before diagnosis. Even if this is so, it is likely that the teeth extracted were usually infected. The American cases reviewed by Anderson and Keefer (1948) further underline the importance of dental sepsis and tooth extraction, for there were 'abscessed teeth' in 33·5 per cent. and tooth extraction in 9·8 per cent. of their 457 'non-haemolytic streptococcal' cases, but in 233 infections due to other organisms an abscessed tooth was blamed as the primary focus in only one, and tooth extraction in only two others. It is likely that dental sepsis is even more common than as reported in either the M.R.C. or the American series. Apical abscesses, in particular, may only be found by X-ray examination, which may be postponed if a patient is ill, and forgotten if he recovers. The danger of leaving dental sepsis untreated was indicated in the case of two patients, one infected with a

micro-aerophilic streptococcus, the other with *Streptococcus viridans*, from whom organisms, indistinguishable from those grown in blood culture before treatment, were grown from tooth roots. The roots were removed in one case at the end of a long course of penicillin, and in the other after finishing such a course. It is questionable whether pregnancy, in itself, is a factor in infection;

TABLE VII

Foci of Infection in an Unselected Group of 215 Cases

	Number of cases	Infecting organism: Strep. viridans	Other streptococci	Enterococcus	H. influenzae	Staph. albus	Other organisms
Tooth extraction before onset	23	23	..	..	..	..	..
Tooth extraction after onset	8	8	..	..	..	..	..
Dental sepsis	60	54*	6	..	..	..	..
Dental caries	12	11	1	..	..	..	..
Tonsils and throat	7	7	..	..	..	..	..
Otitis media	1	1	..	..	..	..	..
'Influenza'	1	1	..	..	..	..	..
Bronchopneumonia	1	1	..	..	..	..	..
Skin sepsis	6	3	1	..	..	2	..
Gall-bladder	1	1	..	..	..	..	..
Post-abortum	1	..	..	1	..	..	..
Post-partum	3	3†	..	..	..	..	..
Pregnancy	9	8	..	..	1	..	..
No focus found	82	66	10	1	1	1	3
Total	215	187	18	2	2	3	3

* One patient also had an infected antrum.
† One patient also had urinary infection.

seven of the nine cases came from one centre interested in heart disease in pregnancy (Jones, Herring, Langley, and Oleesky, 1947), so that the association may have been due to chance. The organism in post-abortum and post-partum bacterial endocarditis is often a staphylococcus or one of the β-haemolytic streptococci (Ramsey and Gillespie, 1941; Dolphin and Cruickshank, 1945), but in the M.R.C. series there were four such cases, three infected with *Streptococcus viridans* and one with an enterococcus.

Mode of Onset

The initial symptoms in a group of 168 patients have been analysed in relation to age, heart lesion, and prognosis. This group consists of all patients treated after March 1946, and also all patients from one centre from the start of the trials; it is therefore statistically 'unselected'.

Symptoms due to infection. 1. *Fever.* Symptoms of fever, such as sweating, chills and shivering, 'influenza', and rigors, were the first complaints of disease in 63 per cent. of patients. Of these symptoms sweating was the most common; only one patient in six had shivering or chills, and only one in 40 had rigors. None of these symptoms could be related to the patient's age, lesion, or final

prognosis. 2. *'Toxaemic' symptoms.* Malaise, tiredness, weakness, and generalized aches and pains were present from the beginning in 40 per cent. of patients, and in half of these there were also febrile symptoms. Sixteen per cent. of all patients complained of early loss of weight, and 4 per cent. noticed pallor. None of these symptoms had any significant relation to age, lesion, or prognosis.

Cardiac symptoms. Nearly 30 per cent. of patients noticed symptoms of heart failure at the beginning of their illness—either dyspnoea on exertion, or swelling of the ankles. Precordial pain was rare (four cases). Under the age of 45 years one-quarter of the patients had symptoms of heart failure at the beginning of their illness, and one-third of these eventually died. Over the age of 45 years one-third had these initial symptoms, but only one out of 12 recovered. The prognostic significance of cardiac failure, which is considerable, is described later.

Peripheral emboli. In 32 cases (20 per cent.) the first symptom was of peripheral embolism. The embolism was cerebral in six cases, and retinal in two; there was pain in the upper abdomen or over the spleen in nine, pain in the back and loin in ten, and pain in one limb or a muscle in five cases. As might be expected, peripheral embolism was most common in acquired heart disease (29 cases), but it carried no prognostic significance.

Pulmonary embolism. In 18 cases (10 per cent.) the illness began with sudden pleural pain, haemoptysis, or other symptoms suggesting pulmonary embolism. This mode of onset occurred in seven of 25 patients (28 per cent.) with congenital heart disease, and had no prognostic significance.

Joint pains. It has been suggested that in subacute bacterial endocarditis rheumatic joint pains, flitting arthralgia, or obvious arthritis means active rheumatism (Matthew and Gilchrist, 1948–9) and that many of the patients with these joint pains have active rheumatic carditis, which contributes to death from congestive heart failure. This view is not supported in the present group. Twenty-nine patients (17 per cent.) complained of joint pains at the onset. Of these 19 recovered, and of the 10 who died death was due to heart failure in only four. Of the other six one died from uraemia, two from embolism, two from haemorrhage, and one from uncontrolled infection. These findings do not prove that rheumatic myocarditis does not play a part in causing death from heart failure; they merely indicate that rheumatic joint pains are not in themselves a bad prognostic sign.

Gastro-intestinal upset. Ten patients (6 per cent.) had gastro-intestinal upsets at the beginning of their illness. The symptoms included anorexia and nausea in five cases, vomiting in four, and diarrhoea in one, and bore no relation to the patient's age or lesion, or to the prognosis.

Headache. Headache was among the first symptoms in nine cases (5 per cent.), but in only one was it severe enough to be described as typical of a 'meningeal' onset. It was not a bad prognostic sign or a warning of later cerebral haemorrhage.

Among other initial symptoms were Osler's nodes or tender finger-pulps in 11 cases, a petechial rash in three, and bruising in one. Three women complained

of amenorrhoea. One patient noticed a swelling behind the jaw, which proved to be a carotid aneurysm.

Physical signs. The incidence of various signs such as petechiae, clubbing, and splenomegaly, occurring during the course of the disease, was not included in this investigation. Four centres have reported these features separately (Smyth and Wilson, 1946; Ward, Meanock, Selbie, and Simon, 1946; Jones, Herring, Langley, and Oleesky, 1947; Matthew and Gilchrist, 1948–9). Complications occurring during treatment were recorded, and are discussed later.

Penicillin Treatment

In the M.R.C. trials several systems of dosage were tried, and the results have already been published; only those findings which have a bearing on present-day therapy will be summarized.

Previously untreated patients. Injections of penicillin every three hours day and night for many weeks are irksome and unpleasant, and because of this some patients still receive inadequate courses of treatment. This danger was clearly illustrated in the early trials, which were designed to show the relative importance of the duration of treatment and of the total amount of penicillin given. Patients were divided into three groups; all were given a total of 5,000,000 units, but the duration of treatment was varied. One group received 1,000,000 units daily for five days, the second 500,000 daily for 10 days, and the third 250,000 daily for 20 days. Treatment failed to eliminate the infection in 83 per cent. of the first group, 50 per cent. of the second group, and 22 per cent. of the third; this clearly showed that, within the limit of this dosage, duration of treatment was of much greater importance than the total amount given. It has since been shown by other workers that very large doses of penicillin are of little value if given only for 10 days (King, Schneierson, Sussman, Janowitz, and Stollerman, 1949). The next part of the trials showed that the daily dose should be large. Three groups of patients were treated for a month; one group received 100,000 units daily, another 250,000 units a day, and the third 500,000 units a day. The results showed that 100,000 units were quite inadequate, and that 250,000 were not so effective as 500,000. After April 1946 a further group of 71 previously untreated patients received 500,000 units daily for 28 days; 14 of these patients (20 per cent.) relapsed or died with the infection uncontrolled, and in only five of these was the infecting organism more than twice as resistant to penicillin as the Oxford staphylococcus. More recently 18 previously untreated patients have received 2,000,000 units daily for between four and six weeks; none has relapsed or died infected. On the basis of these results it was recommended that patients with subacute bacterial endocarditis should be given, as a minimum, 2,000,000 units daily for four to six weeks, however sensitive the infecting organism (Christie, 1949). The treatment of resistant infections is considered in the next section.

Treatment of relapses. Most patients who relapsed were treated again. It was soon found that patients who had once relapsed did not respond so well to

penicillin as those who had not previously been treated. This applied particularly to those who had relapsed after a long course; of 36 such patients who were given a second course of 500,000 units a day for four to six weeks, 15 (41 per cent.) relapsed again or died with uncontrolled infection; and in only three of these was the infecting organism more than twice as resistant to penicillin as the Oxford staphylococcus. Another group of 13 patients who had relapsed after a long course of penicillin were given 2,000,000 units daily for four to six weeks; four of these patients (31 per cent.) relapsed again, but in all four the infecting organism had a high resistance to penicillin—at least 64 times that of the Oxford staphylococcus. One of these patients was eventually cured by 20,000,000 units a day, but another relapsed after 40,000,000 units a day (Cates, 1949). On the basis of these results it was recommended that if a patient had been given an inadequate course of penicillin—for example, 500,000 units a day or less—and then relapsed, he should be given 2,000,000 units daily for six weeks. But if the infecting organism is four or more times as resistant as the Oxford staphylococcus a larger dose may be found necessary, and with very resistant organisms (above 32 times as resistant as the Oxford staphylococcus) infection is unlikely to be controlled by less than 10 or 20 million units daily. The combined use of penicillin and streptomycin in highly resistant infections was first suggested by Hunter (1947), and its value has been confirmed by Robbins and Tompsett (1949). In our experience since the close of the M.R.C. trials this combination is the treatment of choice (Cates, Christie, and Garrod, 1951). With massive doses of penicillin the use of substances such as 'caronamide' and 'benemid', which delay the excretion of penicillin, has to be considered.

Factors predisposing to relapse. It has been seen that 18 previously untreated patients, and 13 patients who relapsed after inadequate treatment, were given 2,000,000 units a day for four to six weeks. Of these 31 patients the four who relapsed had highly resistant organisms. From this small series it appears that, with this system of dosage, the main factor determining relapse is the resistance of the infecting organism to penicillin. With smaller doses of penicillin the resistance of the organism has a less clear-cut relation to the rate of relapse (Christie, 1949). In patients who were given 500,000 units daily for a month the rate of relapse rose after March 1946. This rise suggested that penicillin prepared by the newer methods was less effective than the old product. Manufacturers of the brand most commonly used reported that preparations containing much penicillin K were marketed for three months, after which this defect was corrected. But the higher rate of relapse did not coincide with this fault in manufacture. However, it is impossible to exclude the contention, supported experimentally by Hobby, Lenert, and Hyman (1947), that earlier and cruder preparations of penicillin were more effective *in vivo* than purer preparations.

Time of relapse. In 87 patients the first course of penicillin failed to eliminate the infection, and blood culture either remained positive during treatment or became positive again within six months. Of these patients 67 were treated again, and infection was eventually controlled in 42. Sometimes several courses were given, and altogether penicillin failed to eliminate infection on 142 occasions.

Though the interval between the end of treatment and the relapse of infection, as judged by positive blood culture, varied widely, it was rarely more than a month (Table VIII) and in only 3 per cent. of relapses was it more than two months. In another seven patients, infection, due to an organism similar to that found in the original attack, returned between eight months and 5½ years after

TABLE VIII

Relapses and Uncontrolled Infection

Interval between the end of treatment and positive blood culture. (Patients infected with a different organism, and those 'relapsing' after six months, are shown in Table VI.)

		Number of relapses after treatment lasting	
Positive blood culture		*20 days or more*	*10 days or less*
Persisting during treatment		37	..
Interval (days)	0–10	30	20
	11–20	20	5
	21–30	14	5
	31–60	7	1
	over 60	3*	..

* Relapsed after 63, 130, 134 days.

treatment; in these cases the two organisms were not closely compared, so that it is not possible to say whether they were reinfections or relapses (see *Reinfections*, page 104). The risk of a delayed relapse or reinfection after six months of apparent cure is 2 per cent. per annum.

Complications

Major emboli and other complications were recorded throughout the series. Changes in the heart signs, heart failure, or changes in the state of nutrition during treatment were recorded in the last 139 cases.

Arterial embolism. A major arterial embolism was diagnosed during life in 145 patients (35 per cent.). Autopsy sometimes revealed emboli not recognized during life, but except in the case of coronary emboli the records were not detailed enough to make the findings of value. Altogether 164 embolic attacks were diagnosed in life, 15 patients having two attacks and two having three attacks. The sites and times of these embolisms are set out in Table IX. Sixty-eight of the attacks occurred before treatment began, 45 during treatment, 24 after treatment, and in 27 the time of the attack was not specified. Though 81 of the patients with emboli died, death was due to the embolism in only 17, and partly due to it in another nine. Of the 24 patients who had arterial emboli after treatment had been stopped, infection had not been controlled in eight, and these will not be considered further. One other patient who had a fatal cerebral embolism seven months after treatment died at home, and relapse cannot be excluded. In the remaining 15 patients infection was apparently controlled; in them the intervals between the end of treatment and the attacks were 1, 2, 3, 6, 8, 14, 14, 18, 19, 23, 24, 33, 55, and about 70 days; in the remaining case the date of attack was not specified. In none was auricular fibrillation reported. Of these 15 patients, 12 died shortly after the embolism, death being due to the

embolism in five, and partly due to it in seven; two others died of heart failure many months later. It is therefore clear that the risk of a major embolus remained for several months after apparent cure. The figures also suggest that an embolus occurring in convalescence was often a more serious complication than one occurring during treatment. A possible explanation of this is that, as a vegetation heals, fragments detached from it tend to be firmer and larger;

TABLE IX

Major Arterial Emboli Diagnosed During Life

Site of embolism	*Time of embolism*				
	Before treatment	*During treatment*	*After treatment*	*Not specified*	*Total*
Brain	33	22	12	6	73
Eye	7	2	..	..	9
Coronary	..	3	5	..	8
Spleen	16	10	2	9	37
Kidney	7	1	..	6	14
Mesentery	1	2	2	1	6
Aortic	..	..	1	..	1
Iliac	..	..	1	..	1
Femoral	..	1	..	..	1
Popliteal	3	1	..	..	4
'Leg'	1	1	1	..	3
Axillary	..	..	..	1	1
Arm and forearm	..	1	..	2	3
Not specified	..	1	..	2	3
Total	68	45	24	27	164

this view is supported by the fact that the two largest emboli, one aortic and the other iliac, occurred after treatment. But the figures are too small to justify any definite conclusion, and it may well be that smaller emboli during convalescence were not always reported.

Site of emboli. Seventy patients had cerebral emboli, three having two separate attacks. Thirty-three attacks occurred before treatment, 22 during treatment, and 12 after treatment; in the remaining six the time of the attack was not specified. Forty-seven of these patients died; cerebral embolism was the cause of death in 14, and partly the cause in another two; five others survived the embolism only to die of cerebral haemorrhage later, and in four of these the infection had been apparently controlled for from seven to 16 weeks. Cerebral embolism therefore affected 17 per cent. of all cases, and contributed to 10 per cent. of the deaths, besides maiming some of those patients who survived. Coronary embolism was diagnosed during life in eight cases, and contributed to death in six of these; it was also found *post mortem* in another eight. Fifteen of these patients died, and 12 came to autopsy; the heart-muscle was infarcted in 10, and in the other two a coronary artery was the site of an infected aneurysm or 'abscess'. In 10 cases both mitral and aortic valves were diseased, and in six the mitral valves alone were affected. It seems therefore that coronary embolism did not depend solely on the proximity of vegetations to the mouths of the coronary arteries. Other serious emboli included nine in

the eye, six in the mesentery, and 10 in the aorta, iliac artery, or main blood-vessels to the leg.

Pulmonary embolism. Pulmonary embolism was recorded in 51 patients (12·8 per cent.). In 49 it was diagnosed during life, and in two it was first discovered *post mortem*. Attacks occurred before treatment in 22 cases, during treatment in 18, and after treatment in 12; the time of the attack was not specified in four other patients. Ten patients had more than one attack. Of 45 patients with congenital heart disease 16 (35 per cent.) had one or more pulmonary emboli; three of these 16 patients died, but in only one was death due to the embolism. Of 363 patients with acquired heart disease 35 (10 per cent.) had pulmonary emboli, and 20 of these patients died during or soon after treatment; but death was ascribed to the embolism in only three. Heart failure was the cause of death in another nine of these 20 cases, but seven of the nine patients were already in heart failure before pulmonary embolism occurred. In the remaining eight patients with pulmonary emboli who died, death was due to unrelated causes such as uraemia, infection, or haemorrhage. Pulmonary embolism, then, affected one in three patients with congenital heart disease, and in these cases it was a benign complication. In acquired heart disease it affected one in 10, and seemed to be more often a sequel than the cause of heart failure.

Mycotic aneurysms. Haemorrhage from rupture of a mycotic aneurysm was the main cause of death in 17 patients, and partly the cause in three others. The haemorrhage was cerebral in 16 cases, mesenteric in two, from the femoral artery in one, and into the pericardium in one. In seven of these cases infection had not been controlled by penicillin. Of the patients in whom infection had apparently been controlled, four died from haemorrhage during treatment, six died from cerebral haemorrhage four to 16 weeks after the end of treatment (as mentioned above, embolism preceded the haemorrhage in four of these cases), and another died from cerebral haemorrhage after 22 months of apparent cure. Haemorrhage was not always fatal, even when cerebral. Two patients with subarachnoid haemorrhage were 'cured'; in one the attack was the first symptom of disease, and in the other the bleeding occurred at the end of treatment; a third patient who had subarachnoid haemorrhage before treatment lived for a month after treatment, only to die of another cerebral haemorrhage. Two other patients, one who bled from an aneurysm of the renal artery and another who bled from a femoral aneurysm, were treated successfully by surgery. The clinical course of recognizable aneurysms during penicillin therapy is of interest. In two cases aneurysms stopped increasing in size, and when one was removed it was found to contain organized thrombus. In two other cases penicillin therapy, although otherwise adequate, did not prevent the further expansion of aneurysms, and in one of these a large femoral aneurysm burst during treatment; in the other a large aortic aneurysm stopped expanding after a second course of penicillin. In two other patients a peripheral aneurysm developed after the end of a course of penicillin. The appearance of one coincided with a positive blood culture, and the aneurysm responded to further penicillin therapy. The other case had no further treatment, and remained

apparently cured. The variable behaviour of mycotic aneurysms during penicillin therapy raises the question whether infection may sometimes persist in them after it has been eliminated from the heart vegetations. Pathological evidence suggests that this may be so. Thus in one patient, who died from cerebral haemorrhage after one month's apparent cure, inflammation and organisms were seen in sections of the aneurysm, although no organisms were seen in the heart valves. In another patient, who died from heart failure three months after apparent cure, organisms were seen in sections both of the heart valves and of an unsuspected aneurysm of the renal artery. On the other hand, another patient died of haemorrhage from a femoral mycotic aneurysm after remaining apparently cured for 29 days, and no organisms were seen in the aneurysm, although they were found in sections of heart vegetations; cultures of both sites were sterile. Although the histological findings in these few cases are inconclusive, it would seem that if an aneurysm increases in size in spite of penicillin therapy further penicillin should be given, or the aneurysm should be treated surgically.

Arrhythmias. An arrhythmia was recorded in 20 cases; 18 patients had auricular fibrillation, one had paroxysmal auricular tachycardia, and one a varying heart block. Auricular fibrillation was present before treatment began in eight patients; in four heart failure was present, and three died; in the other four there was no evidence of heart failure, and three of these recovered. Auricular fibrillation developed during treatment in three patients, within a few weeks after treatment in two, and over a year later in four. In one case the time when fibrillation began was not specified. Paroxysmal tachycardia developed shortly after treatment in a patient who died of heart failure; heart block developed in another patient during the treatment of a second attack of endocarditis. Since details of arrhythmia were not specifically sought in this investigation, there may have been other cases; in the authors' own experience eight out of 52 patients (16 per cent.) had auricular fibrillation, two before, two during, and four after treatment. It was not established in any of the M.R.C. cases whether auricular fibrillation preceded the onset of bacterial endocarditis. But as McDonald (1946) has shown, the two conditions are found together more often than is generally recognized, and the presence of fibrillation does not, as is sometimes said, preclude the diagnosis of bacterial endocarditis.

Damage to valves. In 139 cases changes occurring in a heart lesion during life were specially looked for. Evidence of increasing damage of the aortic valve was noted in 11 cases, and of the mitral valve in 10. The changes noticed in aortic lesions were increased incompetence in 10, including rupture of a cusp in two, and the development of stenosis in one. In the 10 patients with changes in a mitral lesion, the murmurs altered in quality in six and became louder in four (in our experience the usual change is that the mitral systolic murmur becomes loud, high-pitched, and musical). Of these patients with signs of increased valve damage, eight with aortic disease and four with mitral disease died; death was due to heart failure in nine, and to uncontrolled infection in three. In the remaining 269 cases changes in the heart lesion were not specially

looked for, but in two it was reported that an aortic cusp ruptured before death; neither patient came to autopsy. Thus changes in heart murmurs during and after treatment were relatively uncommon, being observed in about 15 per cent. of this series; but when they occurred they were a bad prognostic sign, especially if they indicated further damage to the aortic valves. In 89 autopsies, which include only two of the 21 cases mentioned above, severe damage to heart valves was reported in 17 cases (19 per cent.). An aortic cusp had perforated in five cases, had ruptured in one, and had been largely eroded in four; a mitral cusp had perforated in three and had been destroyed in one; chordae tendineae had ruptured in four cases, in one of which there was also a perforated aortic valve. Of these 17 cases, death was due to heart failure in 13, to uncontrolled infection in three, and to embolism in one. Altogether 53 patients who died of heart failure came to post-mortem, and severe damage to valves or chordae tendineae was found in 26 per cent. These post-mortem findings further illustrate the fact that destruction of valves, particularly of the aortic valves, was a grave complication.

Myocarditis. Acute rheumatic fever was the main cause of death in four patients, and was partly responsible in one other; in one of these death occurred 22 months after apparent cure. The true incidence of active rheumatic carditis in the present series is not known, because the detailed histology of the heart-muscle was not included in the investigation. Separate studies made in Belfast (MacIlwaine, 1947) and Edinburgh (Matthew and Gilchrist, 1948–9) revealed that rheumatic myocarditis was common, though sometimes unsuspected during life. Nor do we know the incidence of non-rheumatic myocarditis, which Saphir (Saphir, Katz, and Gore, 1950) stated to be often present at death, although the team in Manchester (Jones, Herring, Langley, and Oleesky, 1947) found severe lesions in five of 13 cases.

Pericarditis. Pericarditis was recognized in seven patients, of whom six died and one recovered. The disease was apparently rheumatic in two, due to coronary embolism in one, and due to spread of infection from a pulmonary aneurysm in one; in three the lesion was described as non-specific.

Renal damage. Uraemia was the cause of death in 18 patients, 10 of whom also had heart failure. Eight of these patients died during treatment, six within a month of treatment, two after five weeks, one after 10, and one after 35 weeks. The underlying renal disease was classed as acute diffuse glomerulonephritis in four cases, subacute nephritis in one, chronic nephritis in two, and pyelonephritis in one; in the remainder details were not given. In Manchester it was found that in the patients who died from causes other than uraemia diffuse glomerular lesions were not infrequent (Jones, Herring, Langley, and Oleesky, 1947). But histological data of the kidneys were not sought in the present investigation, so that the effect of treatment on focal embolic nephritis and on larger renal infarcts can only be inferred clinically. It is well recognized that there is usually some evidence of renal damage in untreated subacute bacterial endocarditis, and before treatment began over 80 per cent. of the patients in St. Bartholomew's Hospital passed red cells and casts in the urine, though these

were sometimes few in number. During treatment microscopic haematuria usually persisted in these patients, and after adequate treatment a few red cells and casts often persisted for several weeks. After six months we found the Addis count rarely outside the limits of normal, but one patient has had microscopic haematuria for three years. A trace of albumin was often present for several weeks after treatment; in one case heavy albuminuria, without other evidence of renal damage, has been present for four and a half years. In the whole M.R.C. series only two patients developed hypertension; in one the original infection was due to *Staphylococcus aureus*, and in the other it was thought that benign hypertension was the underlying cause. It seems, then, that severe renal damage, particularly a diffuse nephritis, may prove fatal in spite of penicillin therapy. Lesser degrees of renal damage usually resolve within a few weeks of treatment, but some evidence of persistent renal damage is occasionally found after a year or more. Whether chronic renal failure will develop in any of these patients only time will tell.

Urinary infections. Early in the M.R.C. trials a few patients developed urinary infections while receiving penicillin. To determine whether this was a coincidence, evidence of a urinary infection was sought in 169 later cases, and was found in 11. In three patients the infection was found before treatment; in two others it was found before treatment under the M.R.C. scheme, but penicillin had already been given elsewhere; in four it developed during treatment, and in two it was first noticed after treatment. The infecting organism was described as coliform or *Bact. coli* in six cases, in two of which there was a second organism, *Staphylococcus albus* in one and *Streptococcus faecalis* in the other; the other organisms were *Ps. pyocyanea*, *Ps. fluorescens*, and *Staphylococcus aureus*, and in two cases the organism was not specified. These findings show that a urinary infection is sometimes associated with subacute bacterial endocarditis, but it is not possible to determine whether the association is causal or casual.

Other complications. Peritonitis was found in three patients at autopsy, and was due in one to rupture of a splenic infarct, and in one to a perforated gastric ulcer; the cause in the third was not specified. Two patients had a hepatitis of unknown origin; both had uraemia as well, and both died after treatment, one after five and one after 10 weeks. Two patients had severe haematemeses; one died, and hepatic cirrhosis was found at autopsy; the other recovered, and the cause was not found. Thrombocytopenia was reported in two patients; both died from heart failure, infection being uncontrolled in one. Of the 45 patients who died with uncontrolled infection, death was attributed to the infection itself in 15.

Causes of Death

Heart failure was the commonest cause of death (Table X). Of the 195 fatal cases in this series it was the main cause in 104 (53 per cent.), and a subsidiary cause in another 19 (10 per cent.). Of the 24 patients who died after six months of apparent cure, death was due to heart failure in 19 (79 per cent.). It has been shown in the previous section that there were several causes for the onset of

TABLE X

Causes of Death

The number of cases in which a subsidiary cause of death was given (32 out of 195 deaths) is given in parentheses.

	Time of death	*Heart failure*	*Arterial emboli*			*Pulmonary emboli*	*Haemorrhage*		*Uraemia*	*Rheumatic fever*	*Pneumonia*	*Other causes*	*Total*
			Cerebral	*Coronary*	*Other*		*Cerebral*	*Other*					
Died with infection apparently controlled	during treatment	15 (7)	7 (1)	1 (1)	..	..	4	1	7	2	2	7	46 (9)
	within one month	23 (6)	3 (1)	(1)	1 (3)	..	1	1	6	(1)	1	1	37 (12)
	within 2nd month	4	1	..	..	1	1	..	1	..	..	..	8
	within 3rd month	11 (1)	..	..	..	..	1	..	1	1	..	..	14 (1)
	within 4–6 months	15 (1)	..	(2)	..	2	1 (2)	..	..	..	..	3	21 (5)
	within 7–12 months	6	1	..	..	..	..	..	1	..	..	1	9
	between 13 and 48 months	13 (1)	..	..	..	..	1	..	..	1	..	..	15 (1)
	Total	87 (16)	12 (2)	1 (4)	1 (3)	3	9 (2)	2	16	4 (1)	3	12	150 (28)
Died with infection uncontrolled	during treatment	6 (1)	..	..	..	..	2 (1)	..	1	..	..	4	13 (2)
	within one month	6	..	1	..	1	..	1	..	..	..	3	12
	within 2nd month	1 (1)	2	..	..	..	1	1	1	..	..	3	9 (1)
	within 3rd month	1	..	..	..	..	1	..	..	..	..	1	3
	between 4 and 7 months	3 (1)	..	..	..	..	..	..	..	..	1	4	8 (1)
	Total	17 (3)	2	1	..	1	4 (1)	2	2	..	1	15*	45 (4)
Total		104 (19)	14 (2)	2 (4)	1 (3)	4	13 (3)	4	18	4 (1)	4	27	195 (32)

* In these 15 cases death was attributed to persistent infection.

heart failure. The most obvious was valve destruction; gross changes in the valves were found in 26 per cent. of the patients who died of heart failure. Another cause was coronary embolism, macroscopic evidence of which was present in 12 out of 89 autopsies (13 per cent.). In two centres it was shown that rheumatic carditis was frequent, though sometimes unsuspected clinically; another centre reported that other forms of myocardial lesions were common. Pulmonary embolism, pericarditis, and auricular fibrillation were contributory factors to heart failure in a few cases. Other causes of death were arterial embolism (13 per cent.), haemorrhage (10 per cent.), uraemia (9 per cent.), rheumatic fever (2 per cent.), pulmonary embolism (2 per cent.), pneumonia (2 per cent.), and other complications (14 per cent.). In 16 per cent. of cases more than one cause of death was reported, and in these cases the subsidiary cause is shown in parentheses in Table X. Details of these fatal complications in patients with controlled and with uncontrolled infection have been discussed in the previous section. The question of persistent infection needs elaboration.

Infection. In 45 of the patients who died infection was uncontrolled, or had recurred after treatment. Most of these patients had received courses of treatment now known to be inadequate. In the remaining 150 fatal cases the infection had apparently been controlled, for blood culture had become negative during treatment and had remained so afterwards, and in nearly every case clinical evidence of infection had subsided. But in these cases the histology of the heart valves suggested that infection had not always been eliminated.

Organisms in 'healed' vegetations. Heart valves were studied histologically in 60 cases in which infection had apparently been controlled (Table XI); 21 of these patients had died during treatment, and 'viable' organisms were seen in nine cases, organisms of uncertain viability in two, and organisms that appeared to be dead in four; in six cases no organisms were seen. The remaining 39 patients had died after treatment with infection apparently controlled, and viable organisms were seen in 10, organisms of uncertain viability in five, and organisms that appeared to be dead in nine cases; in 15 no organisms were seen. Sections of valves were also examined in 14 patients who had died with uncontrolled infection; organisms which appeared to be viable were seen in 10 cases, organisms of doubtful viability were seen in one, and no organisms were seen in three. Cultures were made from the valves in 27 cases altogether (Table XI). Six of these patients had died with uncontrolled infection, and in four cases an organism similar to that which caused the disease was grown. In the remaining 21 patients infection had been apparently controlled; 10 of these died during treatment, and in four cases an organism similar to the infecting organism was grown; the other 11 died after treatment, and an organism similar to the infecting organism was grown in three cases. In general, post-mortem cultures are of doubtful significance, for a variety of organisms, including α-haemolytic streptococci, can often be grown from post-mortem tissue (Epstein and Kugel, 1929). In the present series the post-mortem cultures do not indicate whether 'viable' organisms, found in valve sections from patients who died during convalescence, were in fact alive, because by mischance cultures were made from the valves

in only one of 10 such cases. The presence of these apparently viable organisms cannot yet be explained. Although it is possible that nests of organisms may remain buried in healed vegetations without detriment to the patient, it is

TABLE XI

Bacteria in Heart Valves

	Time of death	*Valve culture*	*Appearance of organisms in sections*				
			'Viable'	*'Uncertain'*	*'Dead'*	*None seen*	*Total*
Died with infection apparently controlled	During treatment	Positive	3	..	1	..	4
		Negative	..	1	3	2	6
		Not done	6	1	..	4	11
		Total	9	2	4	6	21
	Within 1 month	Positive	..	..	..	1	1
		Negative	..	1	2	2	5
		Not done	2	3	1	5	11
		Total	2	4	3	8	17
	2–6 months	Positive	..	..	1	..	1
		Negative	..	..	2	1	3
		Not done	3	1	3	4	11
		Total	3	1	6	5	15
	After 6 months	Positive	1	..	..	..	1
		Negative	..	..	..	..	..
		Not done	4	..	..	2	6
		Total	5	..	..	2	7
	Total	Positive	4	..	2	1	7
		Negative	..	2	7	5	14
		Not done	15	5	4	15	39
		Total	19	7	13	21	60
Died with infection uncontrolled		Positive	2	1	..	1	4
		Negative	1	..	..	1	2
		Not done	7	..	..	1	8
		Total	10	1	..	3	14

Positive culture means that an organism similar to that causing the infection was grown from the heart valve.

Negative culture means that the culture was sterile, or grew contaminants only.

likely that in some of these cases infection was still active. This problem clearly needs further investigation.

Prognosis

From the follow-up results given in Table XII the death-rate during treatment and at intervals after treatment can be calculated by the Life Table technique (Hill, 1950). These death-rates, together with the percentage of patients remaining alive, are shown in Table XIII. Fig. 3 illustrates the proportion of patients still alive at intervals after treatment, expressed as a percentage of those who began treatment. Of the 408 patients 14·5 per cent. died during treatment, and another 27·4 per cent. died in the following six months, leaving 58·1 per cent.

alive. The death-rate then dropped remarkably (Table XIII, column 1) and in subsequent years an average of only 4 per cent. of the survivors died per annum. Expressed in another way, of every 100 patients living six months after the end of treatment 85 were still alive four years after treatment. Tables XIV to XVII show the prognostic significance of various clinical observations made before treatment began.

Table XII

Results of Treatment in 408 Patients

The number of patients who died, who were 'lost', and who were still alive, at intervals after the end of their last course of treatment.

	Died			*Alive*		
					Infection apparently controlled	
	Infection uncontrolled	*Infection apparently controlled*	*Lost*	*Infection uncontrolled*	*Follow-up stopped*	*Follow-up continued*
During treatment . .	13	46	..	32	..	317
In 1st month . .	12	37	..	20	..	280
„ 2nd „ . .	9	8	..	11	..	272
„ 3rd „ . .	3	14	..	8	2	256
„ 4th to 6th month .	7	21	1	1	2	232
„ 7th to 12th „ .	1	9	1	..	13	209
„ 13th to 18th „ .	..	6	2	..	13	188
„ 19th to 24th „ .	..	3	5	..	16	164
„ 25th to 30th „ .	..	3	..	..	12	149
„ 31st to 36th „ .	..	..	..	..	21	128
„ 37th to 42nd „ .	..	2	..	..	31	95
„ 43rd to 48th „ .	..	1	..	..	54	40
Total . . .	45	150	9			

Table XIII

Death-Rates and Survivors

The death-rates during and after treatment are calculated from Table XII. Columns (1) and (3) show the probability of dying (*p*) in each period. Columns (2) and (4) show the survivors, expressed as a percentage of the patients who began treatment. (Patients are not counted in the period in which their follow-up stopped.)

	All patients (408)		*Patients with infection apparently controlled* (363)	
	(1) *p*	(2) % *surviving*	(3) *p*	(4) % *surviving*
During treatment	0·1445	85·5	0·1267	87·3
1st month after treatment . .	0·1403	73·5	0·1167	77·1
2nd „ „ . .	0·0577	69·3	0·0286	74·9
3rd „ „ . .	0·0605	65·1	0·0518	71·0
4th to 6th month after treatment .	0·1073	58·1	0·0830	65·1
7th to 12th „ „ .	0·0456	55·4	0·0413	62·5
13th to 18th „ „ .	0·0309	53·7	0·0309	60·5
19th to 24th „ „ .	0·0180	52·8	0·0180	59·4
25th to 30th „ „ .	0·0197	51·7	0·0197	58·3
31st to 36th „ „ .	0·0	51·7	0·0	58·3
37th to 42nd „ „ .	0·0206	50·7	0·0206	57·1
43rd to 48th „ „ .	0·0244	49·5	0·0244	55·8

Underlying lesion. The effect of the underlying cardiac lesion on prognosis is shown in Table XIV. The lowest death-rate was found in patients with con-

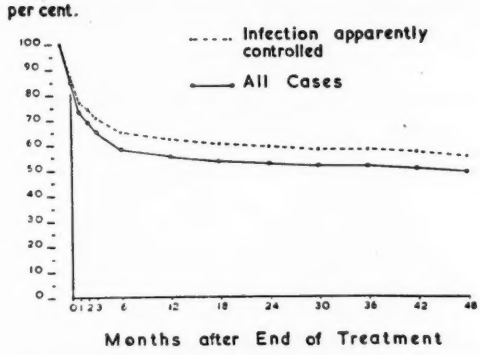

FIG. 3. The proportion of patients alive at the end of treatment and at intervals thereafter. The proportion is expressed as a percentage of those who began treatment. The period of treatment is to the left of the vertical. Calculations are derived from Table XII, using the Life Table technique (Table XIII).

genital lesions (24 per cent.). In patients with acquired heart disease the death-rate was 50 per cent. for all cases, being highest in those with both aortic

TABLE XIV

Relation of Primary Cardiac Lesion to Prognosis

Underlying cardiac lesion		*Number of patients*	*'Cured'*	*Died*	
				Number	%
Acquired	Mitral	169	97	72	43
	Aortic	44	21	23	52§
	Both	143	61	82	57§
Congenital	Ventricular septal defect*†	22	16	6	27
	Ductus†	11	9	2	18
	Others†	12	9	3	25
Uncertain: Bicuspid aortic‡		7	..	7	100
		408	213	195	48

* Two had other congenital lesions as well (Table III).
† One had rheumatic heart disease as well (Table III).
‡ Cases diagnosed *post mortem*; the mitral valve was also involved in two.
§ If patients who by chance were found at autopsy to have bicuspid aortic valves are included, these figures become 57 per cent. for 'aortic' and 58 per cent. for 'both'.

and mitral disease (57 per cent.) and lowest in those with mitral disease alone (43 per cent.).

Heart failure. The presence of heart failure before treatment had a profound effect on prognosis (Table XV). Of those with no heart failure 37 per cent. died,

of those with moderate heart failure 79 per cent. died, and of those with severe heart failure 97 per cent. died. The development of heart failure during treatment was also a bad sign. In an unselected group of 109 patients without heart failure before treatment began, 16 developed heart failure during treatment,

TABLE XV

Relation of Heart Failure to Eventual Prognosis

Degree of heart failure before treatment	*Number of patients*	*'Cured'*	*Died*	
			Number	%
None	314	199	115	37
Moderate	62	13	49	79
Severe	32	1	31	97
	408	213	195	48

TABLE XVI

Relation of Duration of Infection to Eventual Prognosis

Duration of infection (weeks)	*Number of patients*	*'Cured'*	*Died*	
			Number	%
0–9	152	97	55	36
10–19	147	74	73	50
20–29	77	29	48	62
30–39	17	8	9	64
40+	13	3	10	
Not known	2	2		
	408	213	195	48

TABLE XVII

Relation of State of Nutrition to Eventual Prognosis

State of nutrition	*Number of patients*	*'Cured'*	*Died during treatment*	*Died after treatment*	*Died (total)*	
					Number	%
Good	139	93	13	33	46	33
Fair or poor	202	103	26	73	99	49
Bad	44	13	11	20	31	70
Emaciated	23	4	9	10	19	83
	408	213	59	136	195	48

and of these 13 (81 per cent.) died. Heart failure did not develop in the remaining 93, and of these only 17 (18 per cent.) died.

The duration of infection appeared to be significant (Table XVI); of patients recently infected 36 per cent. died, of those infected for 10 to 19 weeks 50 per cent. died, and of those infected for 20 weeks or more 62 per cent. died. It will be seen later that this relationship depended on the higher incidence of heart failure in patients who had been infected for a long time.

The state of nutrition of the patient before treatment was of considerable importance (Table XVII). Of those in a good state of nutrition 33 per cent.

died; when nutrition was fair or poor 49 per cent. died; when it was bad 70 per cent. died; and of patients who were emaciated only four out of 23 (17 per cent.) recovered.

Age. The patients' ages ranged from 7 to 74 years, with a mean of 31·7 years and standard deviation of ±13·1. The mean age of the survivors (29·2

TABLE XVIII

Relation of Age to Prognosis

Five-year age-group	*Number of patients*	*Died*	
		Number	%
5–	5	2	28
10–	13	3	
15–	55	21	38
20–	77	34	44
25–	65	27	41
30–	57	28	49
35–	41	21	51
40–	28	15	54
45–	20	10	50
50–	20	14	70
55–	13	9	
60–	6	5	79
65–	6	4	
70–	2	2	

years) was significantly lower than the mean age of those who died (34·4 years), and the death-rate rose steadily with age (Table XVIII).

Sex. Of the 202 male patients 95 (47 per cent.) recovered, and of the 206 female patients 117 (57 per cent.) recovered. Statistically this difference is barely significant.

Analysis of Selected Cases

The significance of the factors discussed in the preceding section can be judged more accurately if certain corrections are made. To assess their effect on prognosis in adequately treated patients it is necessary to exclude those who died with an uncontrolled infection. To eliminate the error introduced by the different periods of follow-up, results at six months after treatment have been taken; five cases not followed for six months have therefore been omitted. The sixth month has been chosen because deaths after that date were relatively few. This leaves 359 patients in whom infection was apparently controlled, and who either died during treatment or within six months after it, or were alive at the end of that period. An analysis of these cases according to sex, underlying lesion, state of nutrition, and heart failure is set out in Table XIX; except where specified, the figures in this section are derived from that Table.

Underlying lesion. The good prognosis in congenital heart disease was partly related to the fact that heart failure and a bad or emaciated state of nutrition were less common in this type of lesion than in acquired heart disease. But when these factors are excluded, congenital lesions still had a better prognosis than acquired lesions. Thus there were 242 patients without heart failure whose

state of nutrition was better than bad or emaciated; of these 31 had a congenital lesion and two died (6 per cent.), while 211 had an acquired lesion and 44 died (21 per cent.). To a lesser extent the same trend was found in patients with mitral disease alone, compared with those with disease of the aortic, or of both aortic and mitral valves. Thus of the 211 with no heart failure whose state of nutrition was better than bad or emaciated, 105 had mitral disease and 14

TABLE XIX

Correlation of Factors in Prognosis

The results at six months after treatment in 359 patients in whom infection had been controlled. Patients who died during, or within six months after, treatment are shown as a fraction of the total cases in each group. The significance of these figures is discussed in the text.

Degree of heart failure before treatment	*State of nutrition before treatment*	*Underlying lesion*							
		Mitral		*Aortic*		*Both*		*Congenital*	
		M	*F*	*M*	*F*	*M*	*F*	*M*	*F*
None	Good	4/23	3/30	2/12	0/2	5/23	1/13	0/3	0/6
	Fair or poor	3/14	4/38	5/11	1/2	9/20	7/23	0/13	2/9
	Bad	1/4	0/5	1/2	..	3/5	2/4	..	1/3
	Emaciated	1/1	6/7	1/2	..	..	0/1	..	0/1
Moderate or severe	Good	..	1/4	1/2	..	5/5	2/3	0/1	..
	Fair or poor	5/6	5/7	5/6	3/3	11/13	4/6	2/2	..
	Bad	1/1	5/5	1/1	..	1/2	4/4	0/1	0/1
	Emaciated	..	4/4	..	..	..	5/5	..	..
Total		15/49	28/100	16/36	4/7	34/68	25/59	2/20	3/20

(13 per cent.) died, while of 106 with aortic, or both mitral and aortic, disease 30 (28 per cent.) died.

State of nutrition. There was a correlation between the degree of heart failure and the state of nutrition; thus of 277 patients with no heart failure the state of nutrition was bad or emaciated in 35 (13 per cent.), while of 82 with moderate or severe heart failure the state of nutrition was bad or emaciated in 24 (29 per cent.). But the state of nutrition had an effect on prognosis independent of its association with heart failure; thus of the 277 patients with no heart failure before treatment began, 112 were in a good state of nutrition and 15 died (13 per cent.), of the 130 in a fair or poor state of nutrition 31 (24 per cent.) died, of 23 in a bad state of nutrition eight (35 per cent.) died, and of 12 who were emaciated eight (67 per cent.) died.

Duration of infection. In the selected group of patients the duration of infection before treatment clearly affected prognosis (Table XX). Thus when the duration was less than 10 weeks 38 out of 139 patients (27 per cent.) died, when it was between 10 and 19 weeks 46 out of 131 (37 per cent.) died, and when it was 20 weeks or more 43 out of 87 (50 per cent.) died. The longer the duration of infection, the higher was the incidence of heart failure and of an unsatisfactory state of nutrition. When these adverse factors are excluded, the duration of infection is seen to have had little, if any, effect on prognosis, for if we

exclude patients with heart failure and those in a bad or emaciated state of nutrition, the death-rate was 15 per cent. when the duration was less than 10 weeks, 21 per cent. when it was between 10 and 19 weeks, and 26 per cent. when it was 20 weeks or more.

Age. The adverse influence of increasing age, which was clearly shown in the 408 cases, can also be seen in the 359 selected cases followed for six months.

TABLE XX

Duration of Infection

The results at six months after treatment in 359 patients in whom infection had been controlled. The death-rate was higher the longer the infection had been present; this effect was closely related to the increase in heart failure and in unsatisfactory states of nutrition when infection had been present a long time.

Degree of heart failure before treatment	*State of nutrition*	*Duration of infection in weeks*			
		< 10	*10–19*	*20 or more*	*Not known*
None	Good	4/50	8/42	3/19	0/1
	Fair or poor	11/52	11/50	9/27	0/1
	Bad	3/9	2/8	3/6	
	Emaciated	2/2	3/5	3/5	
Moderate or severe	Good	3/6	6/8	0/1	
	Fair or poor	12/15	9/11	14/17	
	Bad	2/4	4/4	6/7	
	Emaciated	1/1	3/3	5/5	
	Total	38/139 (27%)	46/131 (37%)	43/87 (50%)	

TABLE XXI

Age and Prognosis

The results at six months after treatment in 359 patients in whom infection had been controlled. Deaths are shown as a fraction of the total cases in each group. The death-rate was higher in the older age-groups; this effect was closely related to the increase in heart failure in these groups.

	Age-group (years)			
	5–24	*25–39*	*40–49*	*50+*
All cases . . .	41/136 (30%)	45/139 (32%)	18/45 (40%)	21/39 (54%)
Without heart failure .	21/107 (20%)	23/112 (21%)	12/37 (32%)	6/21 (29%)

Thus the death-rate rose from 30 per cent. in patients under 25 years to 54 per cent. in those over 50 years of age (Table XXI). But heart failure was more common in patients over 50 years old, and when patients with heart failure are excluded the death-rate varies little with age.

Sex. In the 359 selected cases there were 173 male patients, of whom at six months after treatment 67 (38·6 per cent.) had died; and there were 186 female patients, of whom 60 (32·3 per cent.) had died within the same period. Although the difference is not statistically significant, analysis of individual groups shows that sex was related to prognosis in two ways. Firstly, mitral disease alone, which carried a better prognosis than other acquired lesions irrespective of sex,

was twice as common in women as in men. Secondly, when the adverse influences of heart failure and emaciation are excluded it is seen that the prognosis was better for female than for male patients, whether the lesion was mitral or aortic or both. Thus of patients with mitral disease 73 were female, of whom seven died (10 per cent.), and 41 were male, of whom eight died (20 per cent.); in female patients with aortic disease there was one death out of four (25 per cent.), and in male patients eight out of 25 (32 per cent.); when both valves were diseased the deaths in female patients were 10 out of 40 (25 per cent.), and in male patients 17 out of 48 (35 per cent.).

Patients with Negative Blood Cultures

During the M.R.C. trials some patients were encountered who appeared to have subacute bacterial endocarditis although their blood cultures were negative. These patients were not included in the trials, although some were given penicillin. At autopsy it was sometimes found that in fact subacute bacterial endocarditis had been present, and in 1947 it was agreed that centres should compile reports on this group of cases. Thirty-four cases were reported by six centres, and results of their treatment have already been published (Christie, 1949).

Significance of negative blood cultures. It is well established that growth may not become evident until after prolonged incubation, and that anaerobic cultures should be made if aerobic cultures are negative. Since these facts were realized when the M.R.C. trials began, considerable significance can be attached to the negative blood cultures. The fact that it is also necessary to repeat blood cultures, if at first they are negative, is illustrated by a group of 83 patients with positive cultures: in 68 (82 per cent.) the cultures were positive at the first attempt, in seven at the second, in seven at the third, and in one at the fourth. Of the 34 cases reported as having negative blood cultures, from three to 10 cultures were made in 23, but for various reasons less than three cultures were made in the remaining 11. In these 11 cases, therefore, the absence of organisms in the blood was not properly established, and they are shown separately in Tables XXII and XXIV. There were no material differences between the two groups, and the clinical features, the response to penicillin, and the post-mortem findings strongly suggest that in both groups, although blood cultures were negative, bacterial infection was usually present.

Analysis of cases. The clinical features, including those on which the diagnosis of bacterial endocarditis was made, are enumerated in Table XXII. All patients except 1 were febrile, the fever in 28 being at least 100° F. There were major emboli in 10 cases and minor emboli in 15, one or the other occurring in 19 patients. Petechiae were noticed in only 10 cases, but clubbing was present in 23, and was gross in nine. Splenomegaly was present in two-thirds of the cases. In no case was the haemoglobin over 90 per cent., and in 23 cases it was below 80 per cent.; but severe anaemia was uncommon, only two patients having 40 per cent. of haemoglobin or less. The erythrocyte sedimentation rate was usually raised, being over 20 mm. per hour in 22, and over 60 mm. in four cases. The Wassermann reaction was positive in two cases and anticomplementary in

TABLE XXII

Patients with Negative Blood Cultures

The clinical features and response to penicillin in 34 patients.

	Number of negative cultures before treatment began	
	3 or more	*Less than 3*
Number of cases	23	11
Sex: male	15	8
female	8	3
Age (years):		
10–19	2	..
20–29	7	2
30–39	8	6
40–49	4	1
50–55	2	2
Underlying lesion:		
Mitral	6*	2
Aortic	5	2
Both	12	7
Rheumatic aetiology	19	9
Degree of heart failure:		
None	6	7
Moderate	12	3
Severe	5	1
State of nutrition:		
Good	3	4
Fair or poor	13	5
Bad	7	2
Fever:		
100° F. or more	20	8
Less than 100° F.	2	3
No fever	1	..
Pulmonary emboli	8	..
Major arterial emboli:		
Cerebral	4	3
Other	2	1
Minor emboli:		
Osler's nodes	2	3
Other	6	4
Petechiae	7	3
Clubbing	17	6
Splenomegaly	16	6
Haemoglobin under 80%	17	6
E.S.R. above 20 mm. per hour	16	6
Renal damage:		
Uraemia	..	3
Red cells in urine	12	5
Only albuminuria	4	..
Response of fever to penicillin:		
Permanent	14	5
Temporary	4	2
Not controlled	5	4
Final result:		
Cured	3	3
Died	20	8

* One with atrial septal defect.

one; all three were men; one had previously received organic arsenic, but there was no evidence *post mortem* of syphilitic heart disease. There was renal damage in 24 patients, in three severe enough to cause uraemia, but the usual finding was merely microscopic haematuria (17 cases). Clinically the underlying heart lesion was thought to have been acquired in 32 of these cases. In one patient it was thought that mitral stenosis and an atrial septal defect were

TABLE XXIII

Results of Treatment in Patients with Negative Blood Cultures

Dosage (daily)	*Number of cases*	*Died with fever controlled*	*Died with fever uncontrolled*	*Fever recurred*	*'Cured'*
2,000,000 units for one month or more	3	2	1	..	..
500,000 units for one month (approx.)	19	8	7	3	1
250,000 units for one month (approx.)	9	2	3	..	4
Unclassifiable	4	1	2	..	1
	35*	13	13†	3	6

* One patient who relapsed and was treated again has been counted as two cases.
† In three patients fever was temporarily controlled but returned before death.

TABLE XXIV

Post-mortem Findings in 15 Cases with Negative Blood Cultures

	3 or more negative cultures	*Less than 3 negative cultures*
Patients examined *post mortem*	8	7
Number with vegetations macroscopically similar to those found in patients who had had positive cultures	6	7
Fibrinoid vegetations	1	..
Granular deposits	1	..
Sections of vegetations:		
Colonies of organisms present	2	4
No colonies present	4	1
Culture of vegetations:		
Strep. faecalis	..	1
Strep. viridans	..	1
Sterile	1	1

present together, and in another an aortic lesion was diagnosed as congenital. This last patient and one other were found *post mortem* to have bicuspid aortic valves. In two patients with mitral valvular disease auricular fibrillation was also present. In these patients with negative cultures the incidence of heart failure before treatment was 62 per cent., compared with 26 per cent. in patients with positive cultures. There was no obvious reason for this difference.

Effect of penicillin. The response to penicillin (Table XXIII) was unsatisfactory in two respects. Firstly, although fever was controlled during treatment in 25 patients, it recurred in six, three of whom later died with their fever

uncontrolled. Secondly, although fever was permanently controlled in 19 patients, only six eventually survived. The death-rate of 82 per cent. can be attributed partly to the high incidence of heart failure, but it was also due to the poor response to penicillin. It seems from these results and from those of others (Loewe and Eiber, 1947) that a more ambitious system of dosage should be used (of the order of 5,000,000 units daily for six weeks), and if the clinical response is unfavourable even larger amounts may be needed. In cases which still prove resistant Wilcox (1950) has shown streptomycin to be of value.

Post-mortem findings. Of 15 cases which came to autopsy (Table XXIV) vegetations similar to those seen in patients who had had positive cultures were seen in 13, while in two others the vegetations were described as 'fibrinoid' or as 'brownish granular deposits'. Sections of vegetations were stained for organisms in 11 of these cases, and colonies were seen in six. In only four were valve cultures made; two were negative, in one *Streptococcus faecalis*, and in another *Streptococcus viridans* was grown. The doubtful meaning of post-mortem cultures has already been discussed. From these findings it seems that most of the cases with negative blood cultures were similar to the abacteriaemic cases described by Keefer (1937) rather than to those in the 'bacteria-free stage' of Libman and Friedberg (1941). That an infection is usually present in the vegetations, although the organism cannot be grown in blood culture, is strongly suggested by the post-mortem findings and by the response of fever to penicillin. The results achieved by Loewe and Eiber (1947), who gave larger doses of penicillin, and by Wilcox (1950) who used streptomycin, support this view.

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Summary

1. Between 1945 and 1948, 442 patients with subacute bacterial endocarditis were treated with penicillin under a scheme organized by the Medical Research Council.

2. Four hundred and eight patients had positive blood cultures before treatment began; 34 patients had negative blood cultures, and are considered separately.

3. The ages ranged from seven to 74 years, but 62 per cent. of patients were between 15 and 35 years of age. The sexes were equally affected. The underlying heart lesion was acquired in 87 per cent. and congenital in 13 per cent. Disease of the mitral valve alone was almost twice as common in female as in male patients, affecting particularly women between 15 and 35 years old. Disease of the aortic valve alone was five times as common in male as in female patients. Disease of both valves affected the sexes equally. The sex incidence of congenital lesions was equal, but ventricular septal defect was commoner in the male, and patent ductus arteriosus in the female sex. Seven patients were found *post mortem* to have bicuspid aortic valves. The aetiology of the acquired lesions was probably rheumatic in 90 per cent. of cases; syphilis was present in four cases, but was the sole cause of the underlying disease in only one. Hypertensive heart disease was the cause in only one case; calcification of valves, though seen in 16 per cent. of autopsies, was usually associated with rheumatic heart disease. In no case was the underlying lesion attributed to myocardial infarction, and in no case was it thought that a previously normal heart was affected.

4. The infecting organism was an α-haemolytic streptococcus in 87 per cent., and a non-haemolytic streptococcus in 7 per cent. In 85 per cent. of cases the resistance of the infecting organism to penicillin was between one-quarter and twice that of the Oxford staphylococcus; in only 4 per cent. was it eight or more times as resistant. Acquired resistance was both uncommon and of small degree. Two patients were infected by two organisms at once, and a third possibly by three.

5. In a representative group of 215 cases a dental focus of infection or a history of dental extraction was present in 48 per cent., and some other focus was found in another 14 per cent.

6. The initial symptoms were those of fever in 63 per cent., heart failure in 30 per cent., peripheral embolism in 20 per cent., joint pains in 17 per cent., and pulmonary embolism in 10 per cent.

7. The results of the M.R.C. trials are reviewed; on the basis of these results it is recommended that the minimum dosage of penicillin should be 2,000,000

units daily for four to six weeks. A larger daily dose should be given if the resistance of the infecting organism is four or more times that of the Oxford staphylococcus. With highly resistant organisms massive doses of penicillin may fail to eliminate the infection. Other methods of treatment, such as the combined use of streptomycin and penicillin which is now in favour, were not studied in these trials.

8. Patients who relapsed did so within 20 days after the end of treatment in 75 per cent., and within a month in 92 per cent. of cases. In seven of the 14 patients who had a second attack between eight months and five and a half years after treatment, the second organism was similar to the first. After six months of apparent cure the risk of a delayed relapse or reinfection is 2 per cent. per annum.

9. There was a major arterial embolism in 35 per cent. of cases; in half of these it was cerebral. Coronary embolism was recognized in 2 per cent. of cases during life, and was found in 13 per cent. of autopsies. The incidence of pulmonary embolism was 35 per cent. in congenital heart disease, and 10 per cent. in acquired heart disease. Auricular fibrillation was recorded at some stage in 4·5 per cent. of cases. Renal damage, unless severe at the time of treatment, usually resolved within a few weeks after it. There was an infection of the urinary tract in 6 per cent. of cases.

10. Of the 195 patients who died, infection had not been controlled, or had recurred, in 45 (23 per cent.); many of these had received inadequate treatment. Heart failure was the commonest cause of death, and was present in 63 per cent. of fatal cases. The remainder died of arterial embolism (13 per cent.), haemorrhage (10 per cent.), uraemia (9 per cent.), pulmonary embolism (2 per cent.), rheumatic carditis (2 per cent.), pneumonia (2 per cent.), and other causes (14 per cent.). There was more than one cause for 16 per cent. of deaths.

11. Valves were stained for organisms in 60 cases in which patients died with the infection apparently controlled; organisms were seen in 39 (65 per cent.) and seemed to be 'viable' in 19 (33 per cent.). The significance of these findings remains in doubt.

12. Of this series of 408 patients 14·5 per cent. died during treatment, and another 27·4 per cent. died in the first six months after treatment. Thereafter the death-rate fell remarkably, and in subsequent years an average of only 4 per cent. of the survivors died per annum.

13. Of the various factors affecting prognosis the presence of heart failure before treatment was the most important. Other factors were age, sex, the site of the lesion and the question whether it was acquired or congenital, the state of nutrition, and the duration of infection.

14. Thirty-four patients with negative blood cultures were given penicillin. In most of these there was good evidence of bacterial infection, for fever responded to penicillin in 25 (73 per cent.), and in one-half of those who came to autopsy organisms were found in the heart valves. Only six cases were 'cured'; this low proportion was due in part to the high incidence of heart failure and in part to inadequate treatment. It is suggested that this type of

patient may need a larger daily dose of penicillin than patients with positive blood cultures.

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CHRONIC MONOCYTIC LEUKAEMIA[1]

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With Plates 16 to 19

The recognition of leukaemia as an entity is generally attributed to the Edinburgh physicians Craigie and Hughes Bennett and to Virchow, who in October and November 1845 described cases *post mortem*. According to Fagge (1886), in the next year the London physicians Fuller and Walshe recognized the leukaemic state during life, and later Virchow (1853), from an examination of unstained blood films, described two forms of leukaemia which he named splenic and lymphatic. It was not until 1913 that Reschad and Schilling-Torgau described a third, monocytic, form of leukaemia, following the differentiation by Schilling (1912) of the monocyte. Monocytic leukaemia is well recognized in the acute form, but chronic cases have rarely been recorded. Dameshek in 1930, reviewing the literature of monocytic leukaemia, found 26 reported cases, but none of more than 12 months' duration. Later Osgood (1937) stated that 11 per cent. of cases of monocytic leukaemia were of the chronic type. We agree with Osgood's criterion that 12 months is the minimum duration which should place the disease in the chronic category, and we here report two cases, one of them of three and a half years' duration. Though true chronic cases have been reported by American authors, including Watkins and Hall (1940), we can find only one in British literature, that of Orr (1933) of about 15 months' duration; but Orr did not explicitly refer to it as chronic. The patient reported by Smith (1937) as having chronic monocytic leukaemia lived less than four months after the onset of symptoms.

Case Reports

Case 1

A retired policeman, aged 55 years, was first seen as an out-patient on February 1, 1946. His chief complaints were shortness of breath on moderate exertion for four months and morning epistaxis for two months. He also complained of the loss of about two stone in weight in the previous five to six months, and of an unproductive cough of four months' duration. On examination he was pale, and a systolic murmur was heard in the mitral and aortic areas. The blood-pressure was 150/75. There were no other abnormal physical signs. A radiograph of the chest and an electrocardiogram were normal. A blood count showed red cells 3·01 million per c.mm., haemoglobin 55 per cent., colour index 0·9, and white cells 4,100 per c.mm., with neutrophils 22 per cent., lymphocytes 65 per cent., and monocytes 13 per cent. (All haemoglobin percentages refer to 14·5 gm. per

[1] Received October 2, 1950.

100 ml. as 100 per cent.) During the next two months there was no response to iron or liver therapy, and the anaemia became more severe. A blood count in April 1946 showed red cells 2·26 million per c.mm., haemoglobin 44 per cent., and colour index 0·85. In view of the resistant anaemia it was thought that

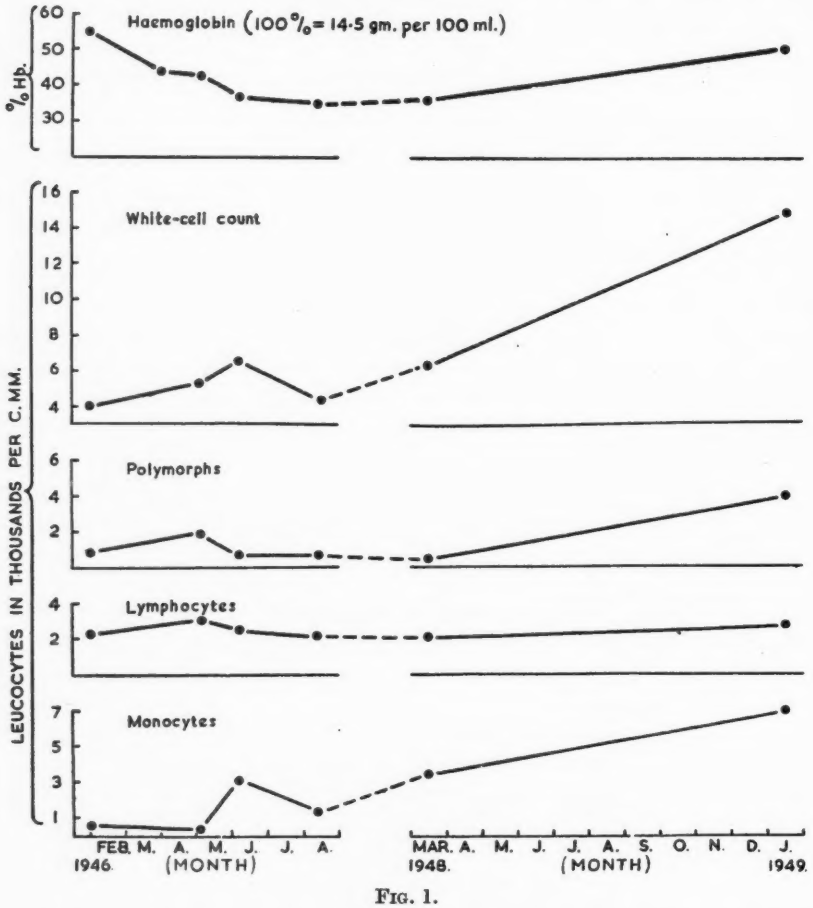

FIG. 1.

further investigations should be carried out, especially with a view to excluding a neoplastic process.

First admission. He was first admitted to hospital in May 1946. The blood count then showed red cells 2·52 million per c.mm., haemoglobin 43 per cent., colour index 0·9, and white cells 5,300 per c.mm., with neutrophils 36 per cent., lymphocytes 58 per cent., monocytes 6 per cent., and reticulocytes 4·25 per cent. In the film a number of giant platelets were noted, and many of the red cells were polychromatic. The sternal marrow was reported as being very cellular but with a normal myeloid-erythroid ratio, and no abnormal cells were noted. A test of the faeces for occult blood was slightly positive, but barium-meal and barium-enema examinations were normal. The fractional test meal, serum-bilirubin level, and liver function tests were normal. The Wassermann reaction

was negative. Radiographs of the femoral bones were normal. Early in June 1946 the blood picture had changed: the red cells were 2·26 million per c.mm., haemoglobin 37 per cent., colour index 0·8, and white cells 6,600 per c.mm., with neutrophils 12 per cent., lymphocytes 39 per cent., monocytes 48 per cent., and eosinophils 1 per cent. There were 2 normoblasts per 100 white cells and

TABLE

Sternal Myelogram of Case 1

	%		%
Neutrophil polymorphs	15·6	Normoblasts B	2·9
Neutrophil stab cells	13·2	Normoblasts C	16·6
Neutrophil metamyelocytes	1·7	Monocytes	19·4
Neutrophil myelocytes	1·6	Promonocytes	6·6
Neutrophil promyelocytes	1·3	Monoblasts	2·4
Myeloblasts	0·5	Vacuolated blast cells	3·4
Eosinophil polymorphs	5·5	Unidentified cells	7·5
Lymphocytes	0·2	Mitoses	0·8
Plasma cells	0·8	Megakaryocytes	None seen

the reticulocytes were 3 per cent. A further examination of the sternal marrow showed it to be moderately cellular, the monocytes being 10 to 15 per cent. of the total cells. No myelogram was done, owing to difficulty in classifying many of the cells. The diagnosis of monocytic leukaemia was considered. In August 1946, when he attended the out-patient department, there was little change in his general condition or blood picture (Fig. 1). In March 1948, after a lapse of 19 months, the patient reported again with symptoms of anaemia. During this long period he had enjoyed comparatively good health. The blood picture remained materially unchanged (Fig. 1).

Second admission. In January 1949 he was readmitted. He stated that six months previously his left ankle had become swollen and painful; this had been followed by a red discoloration of the skin around the joint, which changed through purple to yellow. Subsequently the right ankle had been similarly affected. After a remission both feet had become affected, and he was forced to take to his bed. One morning 14 days before admission, while in bed, he had an attack of left-sided renal colic. The next day painful micturition produced 'dirty urine' containing small dark flecks, and on the following day he had an attack of right-sided renal colic. A day later he passed a stone, which unfortunately he did not save. Examination at the time of admission showed that he was still of good physique, with no evidence of loss of weight. The mucous membranes were pale, and there were palpable axillary lymph-nodes, but no enlargement of the liver or spleen. There were large ecchymoses affecting both lower limbs, especially round the ankle-joints and the dorsum of both feet, with a few petechial haemorrhages over the thighs. The ankles were swollen and tender, and this was considered to be due to haemarthrosis. The leucocyte count was now 15,000 per c.mm., and the platelet count 50,000 per c.mm. Monoblasts (0·33 per cent.) were seen for the first time in the peripheral blood; they were large, often vacuolated, cells with greyish blue cytoplasm and furrowing of the nucleus. There were 2·66 per cent. promonocytes, their greyish cytoplasm displaying many fine azure granules, and their convoluted nuclei containing large nucleoli. Most of the monocytes possessed pseudopodia (Plate 16, Fig. 2), and supravital staining showed characteristic pseudopodial movement and bizarre shapes; they were oxidase-positive. Incubation of the heparinized blood with a small amount of indian ink showed the monocytes to be strongly phagocytic (Plate 16, Fig. 3). A sternal myelogram was as shown in the Table, the salient

feature being the presence of giant vacuolated monoblasts similar to those described in the peripheral blood, but vacuolation was more marked (Plate 16, Figs. 4, 5). Several mitotic figures were seen (Plate 17, Fig. 6). A plain radiograph of the renal tract showed no opaque calculi. The urine contained a moderate amount of albumin, but no abnormality was noted on microscopy of the deposit. The patient was discharged at his own request on January 15, 1949.

Third admission. On February 24, 1949, the patient was admitted again. On this occasion his condition was so poor that interrogation was difficult. All the joints were painful, and vomiting had been practically continuous since a few days after his previous discharge from hospital. On examination he had an earthy colour, and he lay in bed obviously in much pain, resenting movement. There was marked ichthyosis of the skin, with numerous petechial and ecchymotic haemorrhages of the legs. Numerous hard, raised, non-tender red nodules, varying from a quarter to half an inch in diameter, were present on the legs and abdomen, and a few on the arms, neck, and thorax. The face was unaffected. The cervical and axillary lymphatic nodes were moderately enlarged. There was a severe gingivitis, with a few purpuric spots on the palate, and the tonsils were covered with a purulent exudate. The liver and spleen were enlarged to three inches below the costal margins in the nipple lines. Signs of bronchopneumonia were noted in the lung bases, and he died on February 26, 1949, three and a half years after the onset of the symptoms.

Autopsy findings. The lungs showed bronchopneumonia of the lower lobes. The cervical and axillary lymph-nodes were moderately enlarged and rubbery in consistency, and their cut surface was a uniform pale pink. There were petechial haemorrhages on the peritoneum. The liver was enlarged (2,500 gm.) and the cut surface was pale, with yellowish mottling. The spleen was soft and much enlarged, weighing 880 gm.; its cut surface was pale, and the normal markings were obliterated. The intestinal contents were stained with altered blood. The kidneys were enlarged, the right weighing 280 gm. and the left 300 gm.; on section the cortices were pale and showed numerous small nodules, and the calyces contained innumerable small yellow calculi. There was a pale nodule, 1·5 cm. in diameter, on the peritoneal surface of the bladder, to which a segment of small intestine was adherent. The femoral marrow was of a pinkish-red colour throughout. The heart was enlarged and weighed 450 gm., the left ventricle being hypertrophied.

Histology. Sternal marrow. This was obtained within five minutes of death, and showed little change from that examined one month before death, except that the vacuolated blast cells were not so numerous. Special stains for fat and glycogen showed that these giant cells did not contain either substance.

Lymph-nodes. Their architecture was partly destroyed, but several lymphoid follicles with germinal centres remained. Numerous giant cells, 35 to 40μ in diameter, were seen. These cells were actively phagocytic, containing many red cells (up to seven), haemosiderin granules, and even leucocytes (Plate 17, Fig. 7), and were found in the medullary tissue and to a less extent in the peripheral sinuses. Reticulin fibres were not increased. Plasma cells, eosinophils, and numerous monocytoid cells were identified.

The liver was diffusely infiltrated with monocytoid cells, more marked around the portal tracts. Giant phagocytic cells were again prominent.

Spleen. The Malpighian corpuscles were obliterated, and the organ was diffusely infiltrated with similar monocytoid cells and giant phagocytes.

The skin nodules showed solid masses of leukaemic monocytes in the dermis (Plate 18, Fig. 8). Many mitotic figures were seen.

The lungs showed areas of bronchopneumonia, with numerous monocytes

included in the exudate. The alveolar septa were thickened owing to the presence of monocytoid cells (Plate 18, Fig. 9).

The kidneys, bladder nodule, and intestinal mucosa also showed monocytic infiltration.

Case 2

Mrs. E. J., aged 58 years, was admitted to hospital on July 12, 1950, complaining of lassitude and weakness of 13 months' duration, with increasing pallor and breathlessness on exertion for nine months. These symptoms had gradually become more severe, so that she took to her bed two weeks before admission. There was also a weeping skin eruption on the back of her neck of six weeks' duration, and painful and frequent micturition for four weeks before admission. The first illness the patient suffered was in 1938, when she had an operation for repair of a vaginal prolapse. After this she complained of post-prandial dyspepsia, which after repeated investigation was attributed to an anxiety state. For many years she had complained of prolapsed thrombosed haemorrhoids, which never bled. The onset of lassitude and asthenia was in June 1949, when she experienced great exhaustion in looking after her daughter during her confinement. Three months later, in September 1949, her weakness was so severe that she was reluctant to go shopping, finding even the empty shopping basket a burden. In November 1949 her acquaintances remarked on her extreme pallor, and her lassitude and breathlessness were becoming much more marked.

On examination the patient was a well-nourished little woman, with marked pallor of the skin and mucous membranes. Two firm, mobile lymph-nodes were palpable at the posterior border of the left sternomastoid muscle. There were several encrusted lesions at the back of the neck. The fauces were clear. There were a few recent retinal haemorrhages in the left eye. No other abnormal physical signs were detected except thrombotic prolapsed piles. There was no evidence of splenomegaly, hepatomegaly, or generalized lymphadenopathy. Blood examination showed red cells 2·6 million per c.mm., haemoglobin 62 per cent., colour index 1·19, and white cells 28,000 per c.mm., with neutrophils 26 per cent., lymphocytes 22 per cent., monocytes 43 per cent., promonocytes 8 per cent., and monoblasts 1 per cent. The red cells appeared normal, though many were polychromatic. A fractional test meal showed achlorhydria, and a barium meal with follow-through gave a normal result. The Paul-Bunnell test was negative. The urine contained albumin and a few pus and red cells, and yielded a growth of coliform organisms. The patient was treated with sulphonamides (sulphatriad) and a low-grade pyrexia subsided, while the urinary infection and the skin eruption cleared. A slightly raised reddish-purple thickening, about 0·5 cm. in diameter, remained at the back of the neck. Sternal marrow examined on August 14, 1950, was cellular and infiltrated with monocytes, promonocytes, and monoblasts. A large number of these primitive cells of the monocyte series contained large foamy vacuoles closely resembling those in the cells seen in Case 1, though not so large (Plate 19, Figs. 10, 11). The peripheral blood was incubated with indian ink, and again the monocytes were found to be phagocytic towards the particles, but not as actively as in Case 1. Lymph-node biopsy showed the node to be firm and pale in colour. Histologically the architecture was almost lost, a few lymphoid follicles remaining at the periphery. The medulla and sinuses were infiltrated with monocytoid cells showing typical furrowing and convolution of the nuclei (Plate 19, Fig. 12). Perl's stain showed a few endothelial cells of the sinuses to contain haemosiderin, but no giant phagocytes containing the pigment were present. The skin nodule was excised, and showed light infiltration of the dermis with monocytoid cells, particularly

around the hair follicles and sweat glands. The white-cell count rose steadily. On July 27, 1950, there were 34,000 white cells per c.mm., and on August 3 74,000 per c.mm., and the proportion of monocytes, promonocytes, and particularly of blast cells increased. In spite of this the patient's general condition improved, and on August 18 she insisted on returning home. She died fairly suddenly on August 24, 1950, 15 months after the onset of symptoms. No autopsy could be performed.

Discussion

The origin of the monocyte, and the status of monocytic leukaemia, have been debated for the past 38 years. Forkner (1934) mentioned 19 theories regarding the origin of this cell. These theories are variations of the following main views: that of Bloom (1928) and Maximow (1927) of the unitarian school, that the monocyte originates from the lymphoid tissue; that of Naegeli (1931) of the dualist school, who believed the monocyte to arise from myeloid cells in the marrow; and that of Schilling (1926) and others of the trialist school, that the monocyte is derived from the reticulo-endothelial system. The work of Cunningham, Sabin, and Doan (1925) seems to show that the monocyte originates from the primitive reticulum mesenchyme. Good reviews of these theories are those of Evans (1942), of Gittins and Hawksley (1933), and of Clough (1932). Several features of our cases support the Schilling concept. The large vacuolated blast cells seen in the peripheral blood and in the tissues were quite unlike the blast cells of myeloid or lymphatic leukaemia; this vacuolation of cells of the monocytic series was emphasized by Osgood (1937). Abnormal differentiation towards the macrophage type of cell had taken place, and the monocytes of the peripheral blood were more phagocytic towards indian ink than normal monocytes. Increased phagocytosis is not a feature of myeloid or lymphatic leukaemias. The presence in Case 1 of giant phagocytes in the sinuses and medulla of the lymph-nodes suggests a possible origin in this site, with secondary invasion of the germ follicles. We consider these highly phagocytic giant cells to be an essential part of the leukaemic process. Study of the first case makes it difficult to postulate an origin from the myeloid cells of the marrow. If the patient's anaemia indicated the onset of the leukaemic process, the aspiration of normal marrow during the seventh month of his illness may mean that the leukaemic process began outside the marrow, and that the marrow involvement followed later. This view is consistent with the work of Sabin and Doan (1927), who considered that monocytes are not formed in the marrow of rabbits except in pathological conditions. Forkner (1930) considered the origin of the monocytes in rabbits to be the undifferentiated mesenchymal cells of the lymph-nodes. Robb-Smith (1938) was of the opinion that monocytes originate from the primitive mesenchymal cells in the medulla of lymph-nodes. We suggest that the leukaemic process may commence in the lymph-nodes or in the splenic pulp.

The first phase in Case 1 was a normocytic normochromic anaemia, with a slight reduction in the total leucocyte and neutrophil polymorph counts. A similar aleukaemic onset was described by Doan and Wiseman (1934) and Osgood (1937). The next phase was one of comparatively good health, with persistence

of the anaemia and the development of a monocytosis, a state which continued for about two years, although no blast cells were found in the peripheral blood, and the patient showed none of the clinical features associated with leukaemia such as purpura, lymphadenopathy, or splenomegaly. Case 2 also showed the symptoms of a progressive anaemia without clinical evidence of leukaemia. We suggest that the diagnosis of chronic monocytic leukaemia should be considered in cases of persistent and resistant anaemia with monocytosis, even when primitive cells cannot be seen. The cause of the anaemia in leukaemia is uncertain. There are three obvious possibilities: (1) hypoplasia of the erythron due to abnormal differentiation of the primitive mesenchyme cells along leukaemic lines at the expense of erythropoiesis, or due to lack or non-utilization of haemopoietic factors; (2) a myelophthisic anaemia due to infiltration of the marrow by leukaemic cells; (3) increased red-cell destruction or loss. In Case 1 the marrow was not hypoplastic or infiltrated with monocytoid cells at a stage when the anaemia was well established, a fact which is against the first two possibilities. On the other hand, haemosiderosis and erythrophagocytosis were seen in the tissues of Case 1 at autopsy, and the regenerative features of polychromasia and reticulocytosis also indicate the importance of red-cell destruction. Jaffé (1933) considered that the anaemia of leukaemia results from an excessive breakdown of red cells, as shown by the haemosiderosis of the blood-forming organs, although Forkner (1938) thought it impossible to be definite in this matter. In Case 1 chronic blood-loss does not appear to have contributed materially to the anaemia, since the initial epistaxis was not followed by a hypochromic anaemia.

Renal colic is not a recognized feature of leukaemia. In this instance it occurred late, when haemorrhagic manifestations were prominent, and the supposed dark stone may have been a blood clot. But the urinary excretion of uric acid is high in the leukaemias, and since uric acid calculi were found *post mortem* it is more likely that these metabolic stones were the cause of the colic.

Several investigators believe that monocytic leukaemia and the reticuloses are closely related. Custer and Bernhard (1948) found transitions, in a series of lymphatic tumours, between lymphoblastoma, Hodgkin's granuloma, lymphosarcoma, and Hodgkin's sarcoma, and considered the latter disease to be identical with reticulum-cell sarcoma; they also found transitions between Hodgkin's sarcoma and monocytic leukaemia. Gittins and Hawksley (1933) reported bilateral ovarian endotheliomata with reticulo-endotheliosis and monocytic leukaemia in a child of one year. Whitby and Britton (1950) and Forkner (1938) considered reticulum-cell sarcoma to be related to monocytic leukaemia in the same way as lymphosarcoma is related to lymphatic leukaemia. Doan and Wiseman (1934), Osgood (1937), and Dameshek (1933) considered Hodgkin's disease and monocytic leukaemia to be closely related. Doan and Wiseman (1934) found the histological appearance of the lymph-nodes in one of their cases of monocytic leukaemia to be identical with that of Hodgkin's disease. Marchal and Bargeton (1933) experienced difficulty in the histological differentiation between monocytic leukaemia and Hodgkin's disease. No tumour-mass was found in either of our cases. We consider the small nodules

in the skin, kidney, and bladder in Case 1 to have been leukaemic infiltrations. The lymph-nodes in Case 1, though histologically to some extent resembling Hodgkin's disease, had not entirely lost their architecture, and phagocytosis was prominent. The lymph-node in Case 2 consisted almost entirely of monocytoid cells, and was quite unlike Hodgkin's disease.

Acknowledgements

We are indebted to Dr. Leonard Howells and Dr. F. L. Dyson for permission to publish these two cases, and we gratefully acknowledge the helpful criticism and advice of Professor Jethro Gough and Dr. Leonard Howells. We also wish to thank Mr. J. P. Napper for the photomicrographs, and Mr. T. Gray for the graph.

Summary

1. Two cases of chronic monocytic leukaemia are described. In one the disease was of three and a half years' duration and the autopsy findings are given.

2. It is suggested that the cases provide evidence of the separate identity of monocytic leukaemia.

3. Attention is drawn to the prolonged phase of anaemia in both cases, with no clinical evidence of leukaemia. In Case 1 the presence of monocytosis without an increased white-cell count was verified.

4. The relationship between monocytic leukaemia, Hodgkin's disease, and other lymphatic tumours is discussed.

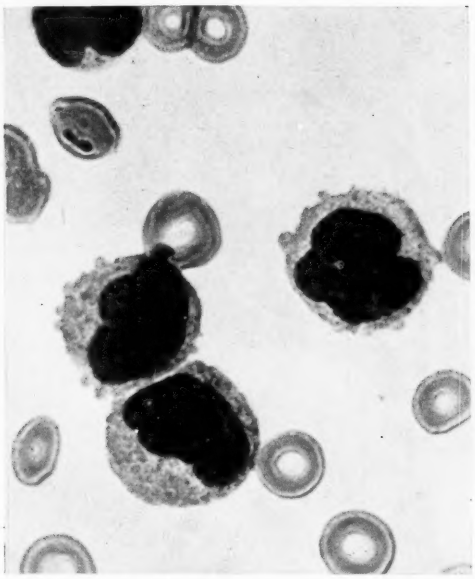

FIG. 2. Case 1. Mature monocytes in peripheral blood, showing typical nuclear structure, and pseudopodial projections (Leishman's stain, × 1,600)

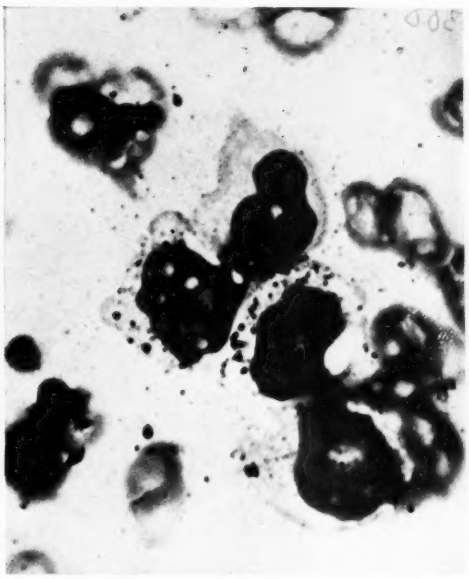

FIG. 3. Case 1. Heparinized peripheral blood, showing phagocytosis of indian ink particles after incubation with a few drops of diluted ink for 20 minutes (× 1,400)

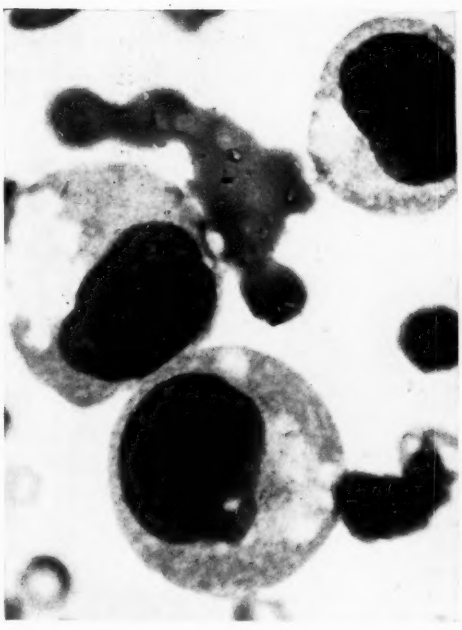

FIG. 4. Case 1. Sternal marrow smear, showing three vacuolated monoblasts (× 1,400)

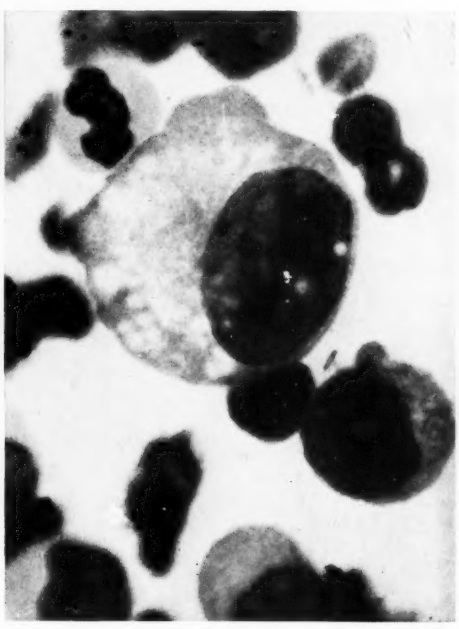

FIG. 5. Case 1. Monoblast showing extreme vacuolation (× 1,400)

FIG. 7. Case 1. Lymph-node showing giant phagocytes with ingested red cells, haemosiderin, and leucocytes (haematoxylin and eosin, × 700)

FIG. 6. Case 1. Giant vacuolated monoblast showing mitosis (× 1,400)

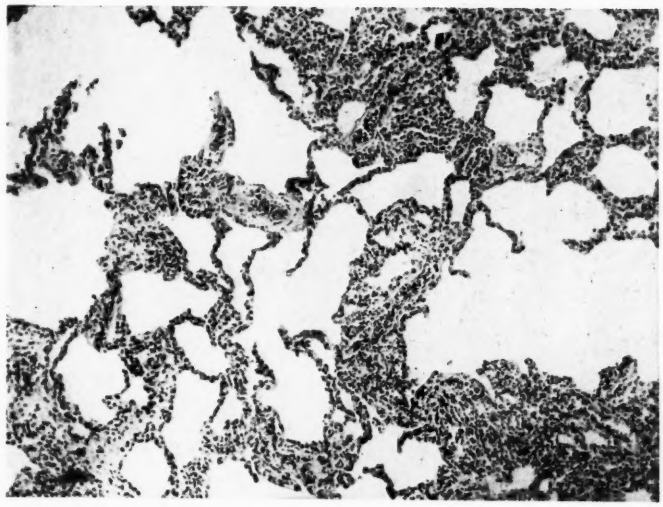

FIG. 9. Case 1. Lung, showing thickening of alveolar septa due to monocytic infiltration (haematoxylin and eosin, × 70)

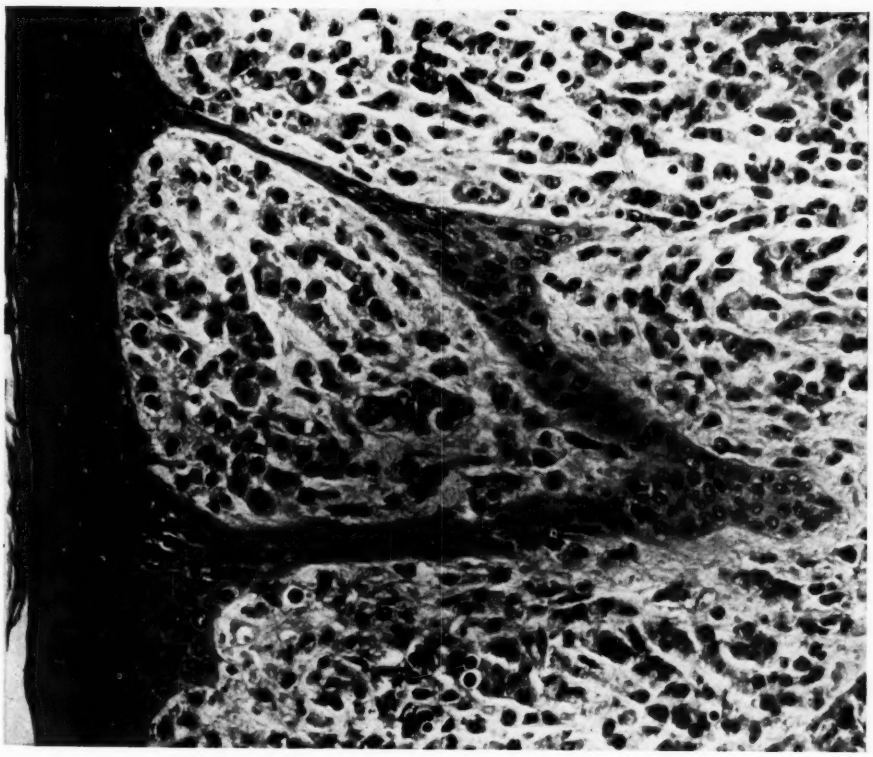

FIG. 8. Case 1. Skin, showing leukaemic infiltration (haematoxylin and eosin, × 250)

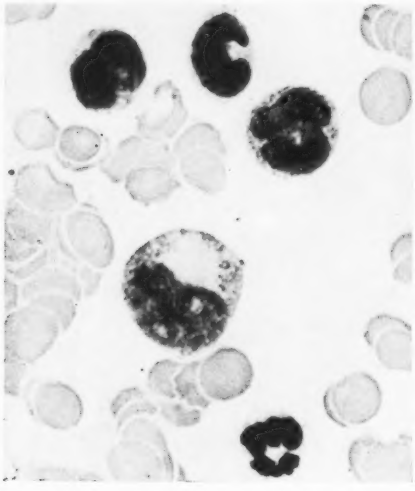

FIG. 10. Case 2. Marrow smear showing vacuolated monoblast and more mature monocytes (× 750)

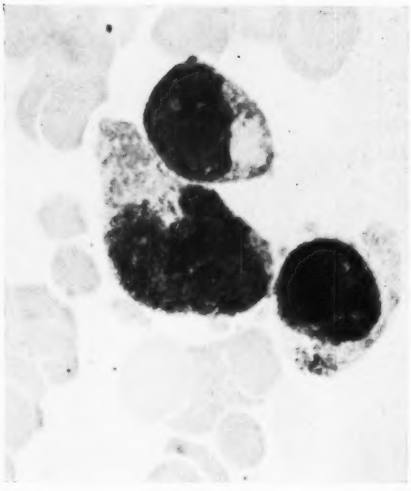

FIG. 11. Case 2. Note the vacuolated monoblast above a mature monocyte (× 1,400)

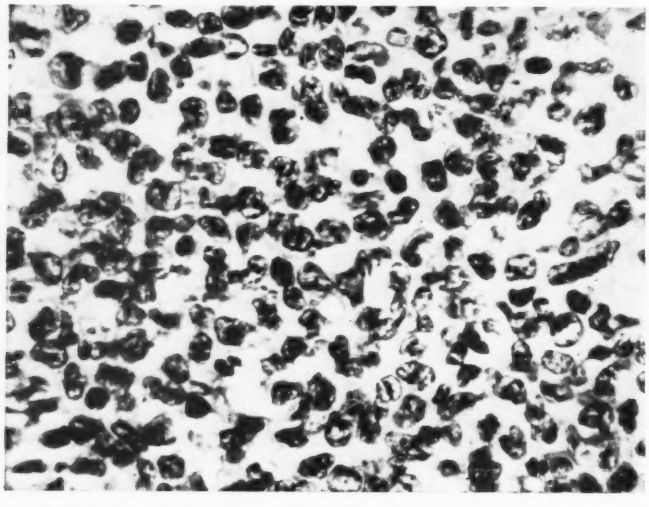

FIG. 12. Case 2. Lymph-node showing monocytoid infiltration. The convoluted nuclei and furrowing can be made out (haemotoxylin and eosin, × 730)

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THE EFFECT OF TOBACCO ON LUNG-VOLUME[1]

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Tobacco has been smoked in England for between three and four hundred years. Up to the first world war the habit was regarded with varying degrees of social disfavour, but despite this fact and the steadily mounting taxation that the smoker has had to bear, the consumption of tobacco in this country has progressively increased, and the amount of money spent on it by the population of Great Britain has now reached prodigious proportions. During the Great Plague of London smoking was regarded as a sure protection against the disease. But the attitude of the medical profession has been in the main to counsel abstention or moderation. Tobacco has been regarded as harmful, and possibly a causal factor, in peripheral vascular disease, coronary artery disease, peptic ulceration, amblyopia, and other diseases. It is, however, only in recent years that quantitative scientific investigation has begun to put our knowledge of the precise effects of tobacco on a secure basis. As examples may be cited the work of Jamieson, Illingworth, and Scott (1946), showing that tobacco has no aggravating effect on ulcer dyspepsia, and that of Wynder and Graham (1950), and Levin, Goldstein, and Gerhardt (1950), showing that cigarette smoking is a factor in the production of bronchial carcinoma, and that pipe smoking plays a part in causing epitheliomata of the lip. Smoking is universally considered to affect the 'wind'. Pugilists, boat-race crews, and athletes when in training invariably eschew tobacco, and people of sedentary habit are apt to attribute their poor exercise-tolerance to excessive smoking. Turley and Harrison (1932), as a result of an investigation of the vital capacity and 'ventilation index' of 75 medical students, 33 of whom were heavy smokers and 42 non-smokers, concluded that tobacco had no adverse effect on ventilatory efficiency; but Short, Johnson, and Ley (1938–9), in an investigation of 2,031 insurance policy holders, found a much higher incidence of cough and exertional dyspnoea in smokers than in non-smokers.

The object of our investigation was to ascertain whether smoking does or does not affect lung capacity. In order to do this we determined the total lung-volume and all its subdivisions in a group of 58 healthy male subjects, and correlated the results with their present and past consumption of tobacco. The vital capacity, complemental air, and reserve air were measured in the usual way on a Benedict-Knipping spirometer, and the closed-circuit constant-volume hydrogen

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(or helium) dilution method described by McMichael (1939) was used for the determination of the functional residual air. All the examinations were carried out in the sitting posture. The subjects included in the investigation were all free from symptoms and signs of respiratory, cardiovascular, and blood disease; all had normal chest X-rays, and none had any disability which could possibly affect their ventilatory efficiency. Many of the subjects examined smoked cigars

TABLE I

Lung-volume of 58 Normal Men related to Past and Present Tobacco Consumption

Division of lung-volume	*Correlation coefficients with tobacco consumption during period*		
	before 1939	*1939–45*	*since 1945*
Total lung-volume	−0·048	+0·002	+0·047
Vital capacity	−0·232	−0·189	−0·228
Complemental air	−0·205	−0·192	−0·222
Reserve air	−0·139	−0·081	−0·110
Functional residual air	+0·102	+0·156	+0·238
Residual air	+0·244	+0·269*	+0·400*
Non-smokers during period	21	13	18
Smokers during period	37	45	40

* Statistically significant (for $n = 58$, a correlation coefficient of 0·258 or greater is significantly different from zero at the 5 per cent. level of significance).

and a pipe in addition to cigarettes; this overlap, and the relatively small total number of subjects, made it impossible to consider cigarette smokers, pipe smokers, and cigar smokers as separate groups. The 'unit of tobacco' was therefore taken as one cigarette; one ounce of pipe tobacco was regarded as the equivalent of 20 cigarettes, and one cigar of three cigarettes. Preliminary inquiries showed that many people smoked considerably more or considerably less during the second world war than before or since. This was not surprising when one considered the alteration in income and in mode of life that the war brought to many people. We therefore considered tobacco consumption during three periods: before 1939, from 1939 to 1945, and since 1945. The correlation coefficients between the present total lung-volume, and its various subdivisions, and tobacco consumption during each of these three periods are shown in Table I. All the 58 subjects are included in each of the three periods, whether they smoked in none, one, two, or all three periods. It will be seen that the total lung-volume shows no appreciable correlation with smoking, but the vital capacity and its two components, the complemental air and reserve air, all show small negative correlations, and the functional residual air and residual air slightly larger positive correlations, during each of the three periods. Of these only the residual air correlations during 1939–45 and since 1945 are statistically significant; but the correlation coefficients show a uniform tendency of the vital capacity, complemental air, and reserve air to diminish, and of the functional residual air and residual air to increase, as tobacco consumption rises. Diminution of vital capacity and increase of residual air have long been known to be closely associated with reduction of ventilatory efficiency, and our results there-

TABLE II

Anthropometric Data and Lung-volume Measurements of the Subjects Grouped according to their Consumption of Tobacco in each of the Three Periods

Volume measurements in litres

Daily tobacco consumption in 'cigarette units'	*Before 1939*								*1939–45*								*After 1945*					
	<5		5–15		16–25		26–80		<5		5–15		16–25		26–80		<5		5–15		16–25	
Number of subjects	21		10		15		12		14		19		13		12		19		26		23	
	mean	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*	*mean*	*s.d.*
Age (years)	25·76	14·42	41·80	13·27	49·67	11·73	47·17	11·77	24·57	15·71	40·26	14·50	50·46	14·62	42·08	12·57	31·74	18·76	40·35	15·65	47·54	13·53
Height (inches)	67·00	3·87	67·30	1·89	66·47	3·02	66·33	2·35	66·50	4·17	66·68	2·06	68·00	3·19	65·92	2·61	66·74	4·01	66·77	2·31	66·85	3·11
Weight (pounds)	132·57	26·58	139·40	16·15	133·67	15·35	138·58	20·21	134·50	29·37	134·21	17·29	135·23	13·82	137·90	22·91	134·37	26·11	135·46	16·87	136·23	22·21
Chest expansion (inches)	3·40	0·85	3·03	0·67	2·90	0·93	3·10	0·76	3·36	0·89	3·09	0·73	3·13	0·83	2·42	0·95	3·33	0·97	3·10	0·72	2·94	0·61
Radiological chest-volume	13·44	2·91	14·48	1·15	13·58	2·17	14·63	1·66	13·28	3·43	13·84	1·22	14·33	2·39	14·23	1·78	13·84	3·31	14·00	1·36	13·78	2·09
Total lung-volume	5·66	1·22	6·00	0·91	5·29	0·83	5·79	0·69	5·59	1·41	5·69	0·82	5·65	1·00	5·65	0·64	5·62	1·29	5·58	0·86	5·60	0·80
Vital capacity	4·18	1·01	4·07	0·56	3·58	0·65	3·72	0·70	4·20	1·14	3·85	0·66	3·89	0·75	3·69	0·60	4·12	1·08	3·96	0·61	3·51	0·67
Complemental air	2·95	0·79	2·65	0·52	2·41	0·38	2·59	0·46	2·93	0·72	2·63	0·43	2·64	0·56	2·53	0·73	2·89	0·69	2·68	0·60	2·40	0·43
Reserve air	1·23	0·50	1·42	0·54	1·17	0·37	1·12	0·41	1·27	0·24	1·22	0·51	1·25	0·37	1·16	0·47	1·23	0·46	1·28	0·53	1·11	0·35
Functional residual air	2·71	0·85	3·35	0·83	2·88	0·62	3·20	0·52	2·66	0·85	3·06	0·75	3·02	0·61	3·12	0·80	2·73	0·78	2·92	0·86	3·20	0·50
Residual air	1·48	0·54	1·93	0·70	1·71	0·51	2·07	0·40	1·39	0·55	1·84	0·62	1·76	0·49	1·96	0·52	1·49	0·57	1·63	0·66	2·09	0·35

fore suggest that smoking may have a slight deleterious effect in this direction. It will be noted that the correlation coefficient of residual air in the period since 1945 is higher than in that from 1939 to 1945, and higher in the 1939–45 period than in the period before 1939. This suggests that any changes that may be produced by tobacco are not irreversible, and that ventilatory efficiency improves when the habit is given up. In a previous communication (Whitfield,

TABLE III

Anthropometric Data in relation to Smoking

	Correlation coefficients with tobacco consumption during the period		
	before 1939	*1939–45*	*after 1945*
Age	+0·423	+0·286	+0·345
Height	+0·057	−0·194	+0·056
Weight	+0·030	−0·035	+0·145
Chest expansion	−0·156	−0·594	−0·123
Radiological chest-volume	+0·097	+0·058	+0·067

Waterhouse, and Arnott, 1950) we have shown that if the age, height, weight, chest expansion, and radiological chest-volume are known, the total lung-volume and all its subdivisions can be predicted with a high degree of precision in normal subjects. The comparison of lung-volumes predicted from these anthropometric data with the observed values might have given valuable confirmatory evidence of the trends shown in Table I, but unfortunately the 58 subjects whom we examined during the investigation of the effects of tobacco were also used for the calculation of the prediction formula, and in those calculations tobacco consumption was disregarded. We were not surprised, therefore, to find virtually no discrepancy between the predicted and observed values.

In order to confirm the above impressions regarding the effect of smoking on lung-volume, we have for each of the three periods divided our subjects into groups according to the magnitude of their tobacco consumption, and have calculated the mean values of the total lung-volume and all its subdivisions for each group. The results obtained are shown in Table II, which also shows the mean age, height, weight, chest expansion, and radiological chest-volume of each group. As would be expected, the trends evident in Table II are similar to those shown in Table I. For each of the three periods the total lung-volume is unaffected by the amount of tobacco consumed, but the vital capacity and complemental air show a progressive decrease, and the functional residual air and residual air a progressive increase, as tobacco consumption rises. These changes are especially evident in the period after 1945, again suggesting that current smoking is more important than past indulgence. It will also be noticed that the mean height, weight, and radiological chest-volume for each period and subgroup are virtually the same, but in each of the periods the mean chest expansion decreases and the mean age increases with tobacco consumption. We ourselves (Whitfield, Waterhouse, and Arnott, 1950) and previous workers (Robinson, 1939; Kaltreider, Fray, and Hyde, 1938; Aslett, Hart, and McMichael, 1939)

have shown that vital capacity decreases and residual air increases with age. We were therefore forced to consider whether the changes we were attributing to tobacco were actually the result of age, and unrelated to smoking, particularly in view of the findings of Jamieson, Illingworth, and Scott (1946) who, in their investigation of the effects of smoking on peptic ulcer, concluded that aggravation apparently due to tobacco was in fact due to increasing age. We therefore

TABLE IV

Vital Capacity and Residual Air in relation to Smoking, with the Effects of Age Removed

	Correlation coefficients with smoking during the period					
	before 1939		*1939–45*		*after 1945*	
Division of lung-volume	*age disregarded*	*effects of age removed*	*age disregarded*	*effects of age removed*	*age disregarded*	*effects of age removed*
Vital capacity	−0·232	−0·065	−0·189	−0·078	−0·228	−0·097
Residual air	+0·244	+0·115	+0·269	+0·189	+0·400	+0·318

calculated the correlation coefficients between age and smoking during each of the three periods. The results obtained are shown in Table III, which also includes the correlation coefficients between smoking and height, weight, chest expansion, and radiological chest-volume. It will be seen that there is no correlation between smoking and height, weight, or radiological chest-volume. There is, however, an appreciable and uniformly negative correlation between chest expansion and smoking, suggesting that the habit may reduce the capacity to expand the chest; and there is also a uniformly positive correlation between smoking and age, which is for each of the periods greater than all but one of the correlation coefficients obtained between smoking and the various divisions of lung-volume (Table I). This result suggested that age might well be responsible for the changes in lung-volume apparently attributable to tobacco. We therefore calculated the partial correlation coefficients between smoking and certain divisions of lung-volume with the effects of age removed. The results are shown in Table IV. It will be seen that age is the major factor in the reduction of vital capacity in each of the three periods, but that tobacco is to some extent responsible and that the part it plays is greater in the periods 1939–45 and after 1945 than it is in the period before 1939. But the increase in residual air is seen to be due more to tobacco than to age, and the greatest effect of smoking comes from the period after 1945, the least from the period before 1939. In other words, smoking produces a small diminution in vital capacity and a more pronounced increase in residual air and, as we have inferred above, these changes are greatest in subjects whose present and recent consumption of tobacco is high.

The importance of the ratio of residual air to total lung-volume as an index of ventilatory efficiency is widely recognized, and has been stressed by many previous writers (Meakins and Christie, 1929; Hurtado and Boller, 1933; Hurtado, Kaltreider, Fray, Brooks, and McCann, 1934; Kaltreider, Fray, and

Hyde, 1938; Aslett, Hart, and McMichael, 1939). We therefore calculated the correlation coefficients between the ratio $\frac{\text{residual air}}{\text{total lung-volume}}$ and smoking, and

TABLE V

Residual Air as a Percentage of Total Lung-volume, of Vital Capacity, and of Complemental Air, in relation to Smoking

	Correlation coefficients with smoking during the period					
	before 1939		*1939–45*		*after 1945*	
	age disregarded	*effects of age removed*	*age disregarded*	*effects of age removed*	*age disregarded*	*effects of age removed*
$\frac{\text{Residual air}}{\text{Total lung-volume}}$	+0·314	+0·147	+0·307	+0·206	+0·444	+0·341
$\frac{\text{Residual air}}{\text{Vital capacity}}$	+0·299	+0·115	+0·286	+0·174	+0·437	+0·327
$\frac{\text{Residual air}}{\text{Complemental air}}$	+0·252	+0·072	+0·337	+0·243	+0·431	+0·327

also the partial correlation coefficients with the effect of age removed. The results are shown in Table V, which also includes the correlation coefficients between smoking and the ratios of residual air to vital capacity and to complemental air, to which reference is sometimes made. The correlation coefficients between smoking and residual air are uniformly positive in all three periods, both when the effects of age are disregarded and when they are removed, and no matter whether residual air is considered as a percentage of total lung-volume, of vital capacity, or of complemental air. The proportionate influence of age and tobacco is similar to that noted when the absolute values were considered. This result confirms our previous conclusion that smoking increases residual air, and the increase in the ratio of residual air to total lung-volume is strong evidence that smoking impairs ventilatory efficiency. Once again the correlation coefficients are highest in the period after 1945 and lowest in that before 1939, further confirming our hypothesis that it is recent rather than past smoking which affects lung-volume.

Acknowledgements

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Summary

1. The total lung-volume and all its subdivisions have been determined in 58 healthy men, and the results have been correlated with their present and past consumption of tobacco.

2. Smoking produces a slight diminution in the vital capacity and a more pronounced increase in the residual air and in the ratio of residual air to total lung-volume.

3. These effects are much more evident in subjects whose recent consumption of tobacco has been high.

4. Smoking also produces a diminution in chest expansion.

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URAEMIA COMPLICATING LOW SALT TREATMENT OF HEART FAILURE[1]

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The use of mercurial diuretics constitutes one of the greatest advances in the treatment of heart disease since the introduction of digitalis. For many years the customary treatment of heart failure in this medical unit consisted of complete rest in bed, appropriate doses of digitalis, restriction of fluid intake to three pints daily, and injections of the mercuramide preparation 'neptal'. These injections were given on alternate days until visible oedema had gone, for a further four doses to abolish latent oedema, and then as often as necessary to prevent reaccumulation. In many cases of heart failure the urine, on the patient's admission to hospital, contained albumin, casts, and red blood-cells, the blood-urea was considerably raised, and urea clearance tests gave poor results. The administration of neptal to such patients was regularly followed by improvement of renal function as well as of the heart failure, and mercurial diuretics were therefore withheld only in cases complicated by gross renal failure. During a period of 16 years no deaths from renal failure were recorded in which it was felt that the mercurials were responsible. It has been known since 1920 (Saxl and Heilig) that the mercurial diuretics promote the excretion of sodium even more potently than that of water. More recently it has become the custom to restrict salt intake, thereby still further promoting salt-depletion and hastening the loss of oedema. In 1948 a diet containing 0·2 gm. of sodium per day was adopted in this unit. Fluid restriction was no longer practised. During May 1948 four patients became uraemic (Cases 1 to 4), and one (Case 1) died of this complication. In the other three recovery from uraemia followed the restoration of a normal diet, though all died later from other causes. A further uraemic death occurred shortly afterwards (Case 5). A review of these cases (Table I) showed that four of the five were hypertensive, and four were over the age of 60. In Case 1, although no casts were found in the urine, tubular function as measured by the urea concentration test was impaired. In the remaining cases renal function was initially normal or nearly normal, in spite of albuminuria and the presence of urinary casts in Cases 3, 4, and 5. In the light of previous observations referred to above in similar cases, it was considered unlikely that the uraemia in these patients was the result of structural damage by neptal to the kidneys. It seemed more likely that the condition was due to salt-depletion.

[1] Received August 31, 1950.

Investigations and Results

Evidence was sought in support of the two alternative mechanisms, (1) structural damage to the kidney, (2) salt-depletion leading to functional renal impairment.

1. *Evidence of renal structural damage*

(*a*) *Post-mortem material.* Microscopic examination of the kidneys in Cases 1 to 5 showed arteriosclerosis of the medium-sized arteries, often with reduplication of the internal elastic lamina. Most of the glomeruli appeared normal,

TABLE I

The Aetiology of Heart Failure and Results of Renal Function Tests in Cases 1 to 5

Case number	*Sex*	*Age (years)*	*Aetiology of heart failure*	*Albuminuria*	*Microscopic deposit*	*Urea clearance (% of normal)*	*Maximum urea concentration (gm./100 ml.)*	*Blood-urea on admission (mg./100 ml.)*
1	M	68	Hypertension	0	0	29	0·70	80
2	M	73	Coronary occlusion	0	0	..	2·45	45
3	F	69	Hypertension Coronary disease	Trace	Occasional granular casts	46	1·70	48
4	M	62	Hypertension	Trace	Scanty granular, hyaline, and epithelial casts	64	2·30	20
5	M	56	Hypertension	Moderately heavy	Hyaline, epithelial, and granular casts	96	2·65	58

though some were hyalinized. The majority of the tubules appeared normal, though a few showed slight epithelial desquamation. There was no blockage of the tubular lumina by desquamated epithelium. There were a few areas of fibrosis, with disappearance of glomeruli and tubules. In general, the appearances were those which are commonly seen in persons with arteriosclerosis and high blood-pressure in whom no evidence of renal failure has ever appeared.

(*b*) *Evidence obtained during life.* All subsequent patients receiving mercurial diuretics were examined for evidence of structural damage to the kidneys occurring during treatment. The methods adopted were measurements of the daily loss of protein in the urine and daily counts of the urinary casts.

Daily loss of protein. All the urine passed by each patient was collected in separate 24-hour periods. The protein content was measured at first by Esbach's, and later with greater accuracy by Kjeldhal's method for four or five days before the use of neptal, and then throughout the whole period of treatment. There was no constant relation between loss of protein and neptal injections, either in those who developed uraemia or in those who did not. In patients with heart failure who responded well to treatment the loss of protein steadily diminished.

Urinary casts. The number of casts in each 24-hour specimen of urine was estimated by Addis's technique (1925). Often there was an increase of casts in the 24 hours following neptal. Addis (1926) showed that casts are better preserved in a specimen of urine containing a high concentration of salt, and the increased counts on the days of neptal injections may have been due to better preservation of the casts by the higher salt concentration. There was a general tendency for the number of casts excreted to fall as the heart failure improved, even in the patients who developed uraemia.

2. *Evidence of salt-depletion*

Serum-chloride estimations. Table II shows the results of daily serum-chloride estimations in three representative cases. After each injection of neptal there

TABLE II

Serum-chloride and Urinary Chloride Output during Low Salt Treatment of Heart Failure

The measurements cover 14-day periods in three representative cases. The patients were having a low sodium diet, and received injections of neptal at 7.30 a.m. on the days marked *.

Patient C.H. (Day 1 = 12.11.48)			*Patient T.B. (Day 1 = 5.10.48)*			*Patient D.M. (Day 1 = 11.10.48)*		
Day	*Serum-chloride (mg./100 ml., as NaCl)*	*Urinary chloride output (gm./24 hrs., as NaCl)*	*Day*	*Serum-chloride (mg./100 ml., as NaCl)*	*Urinary chloride output (gm./24 hrs., as NaCl)*	*Day*	*Serum-chloride (mg./100 ml., as NaCl)*	*Urinary chloride output (gm./24 hrs., as NaCl)*
1	610	..	1	625	..	1	615	7·3
2	600	0·96	2*	620	12·4	2	600	6·0
3	565	0·9	3	590	...	3	620	1·5
4	560	1·0	4	600	3·8	4	580	1·5
5	550	0	5	585	..	5	580	2·1
6*	540	9·2	6	..	1·7	6	590	1·5
7	500	0·3	7*	590	10·9	7	..	1·7
8*	485	5·1	8	550	0·5	8*	580	7·8
9	470	0	9	550	0·2	9	570	2·0
10*	..	0·9	10*	565	5·2	10*	..	2·1
11	490	0·5	11	545	0·4	11	505	0·4
12	485	0	12	550	0·9	12*	530	1·2
13	480	0·4	13*	555	6·4	13	530	..
14*	490	..	14	525	0·1	14*	..	1·2

was a fall in serum-chloride, with perhaps a slight rise on the days between injections. Ultimately values well below normal were found in most cases. This effect had previously been noted by Crawford and McIntosh (1925) and by de Graff and Nadler (1942).

The daily urinary chloride excretion was determined by Harvey's method (1910). The concentration of chloride, as well as the volume of urine, increased on the day of the neptal injections. Occasionally there was an increased ex-

cretion of salt without a water diuresis. Eventually the urinary chloride concentration fell to values of less than 0·5 gm. per litre, which Marriott (1947) has shown to indicate severe salt-depletion. The fact was thus confirmed that mercurial diuretics, combined with a low salt diet, can lead to salt-depletion

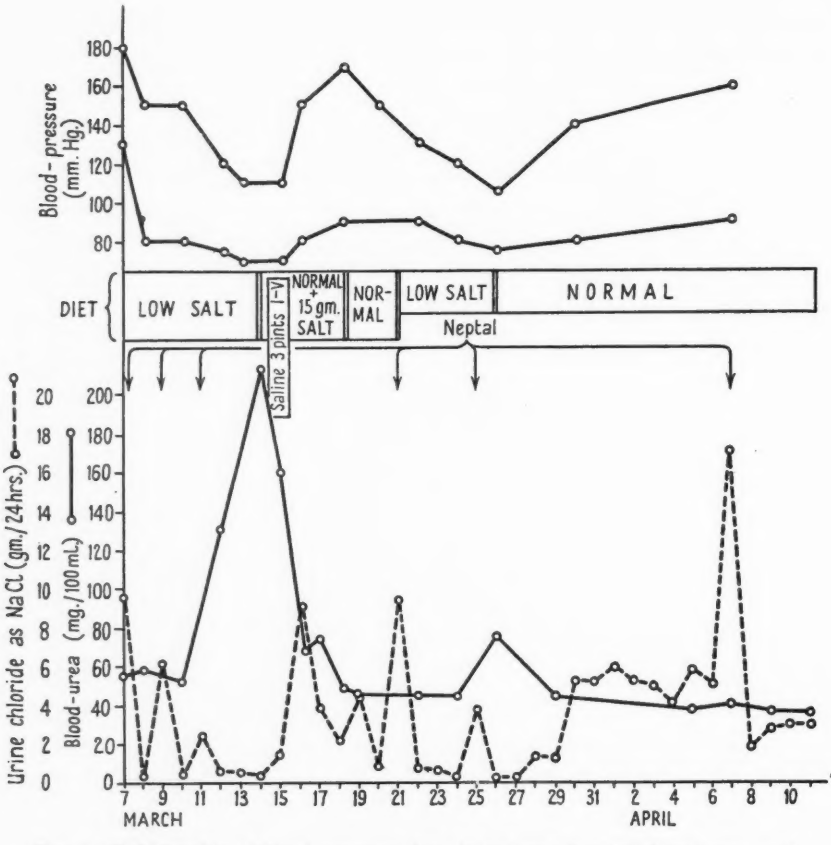

FIG. 1. Relationship of blood-pressure, diet, injections of neptal, blood-urea, and urinary chloride output over a period of 36 days in Case 6.

even in patients with congestive cardiac failure and oedema. It is noteworthy that salt-depletion may occur, as in Case 5, at a time when the patient still has oedema and ascites.

Observations on the evolution of the salt-depletion syndrome in three further cases. During the months March to June 1949, Cases 6, 7, and 8 developed uraemia while under observation. Fig. 1 shows the relationship between blood-pressure, diet, neptal injections, blood-urea level, and daily urinary chloride output over a period of 36 days in Case 6. Two periods of salt-depletion, shown by a low urinary output of chloride, were marked by a raised blood-urea and hypoten-

sion. During the first period the patient complained of lassitude, nausea, anorexia, and orthostatic faintness, and was very drowsy. When the blood-urea was at its highest level of 215 mg. per 100 ml., three pints of physiological saline were given intravenously, and within six hours there was marked sub-

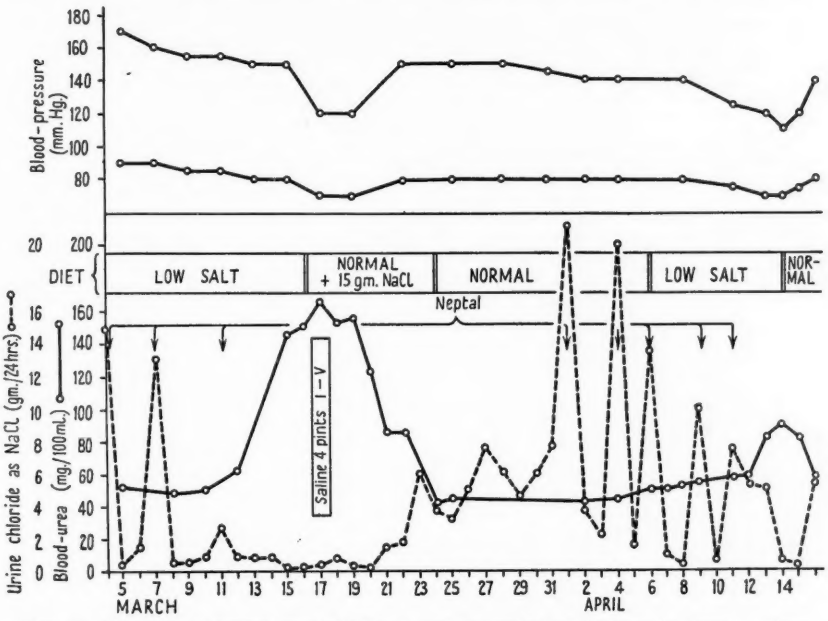

FIG. 2. The same observations (cf. Fig. 1) over a period of 43 days in Case 7. Four pints of intravenous saline were given again on April 14.

jective improvement. During the next three days the patient received 15 gm. of sodium chloride by mouth in addition to a normal diet, and the blood-urea fell to normal, while clinical improvement was maintained. A week after his recovery from this episode a low salt diet was resumed, and two further injections of neptal were given. A second period of salt-depletion ensued, the blood-pressure again fell, and the blood-urea rose from 48 to 78 mg. per 100 ml. There were no accompanying symptoms, and therefore no intravenous saline was given, but a normal diet was substituted and neptal was withheld for 12 days. During this period the urinary chloride excretion returned to a normal figure of 5 to 6 gm. in 24 hours, and the blood-urea returned to normal. In contrast to Case 5, both periods of salt-depletion in this patient occurred after visible oedema had disappeared. Salt replacement was not followed by a reappearance of oedema. Fig. 2 shows the same relationships over a period of 43 days in Case 7. The first period of uraemia was accompanied by drowsiness, lethargy, and mental confusion. Throughout this period there was hypotension, and the urinary chloride output revealed salt-depletion. Treatment with four pints of physiological saline given intravenously, followed by a normal diet with added salt, led to a return of the urinary chloride output and blood-urea

to normal within a week. During 12 days on a normal diet two further injections of neptal were given without adverse effect. The low salt diet was then deliberately reintroduced, and as the urinary chloride output declined the systolic and diastolic blood-pressures fell, and the blood-urea increased. When the blood-

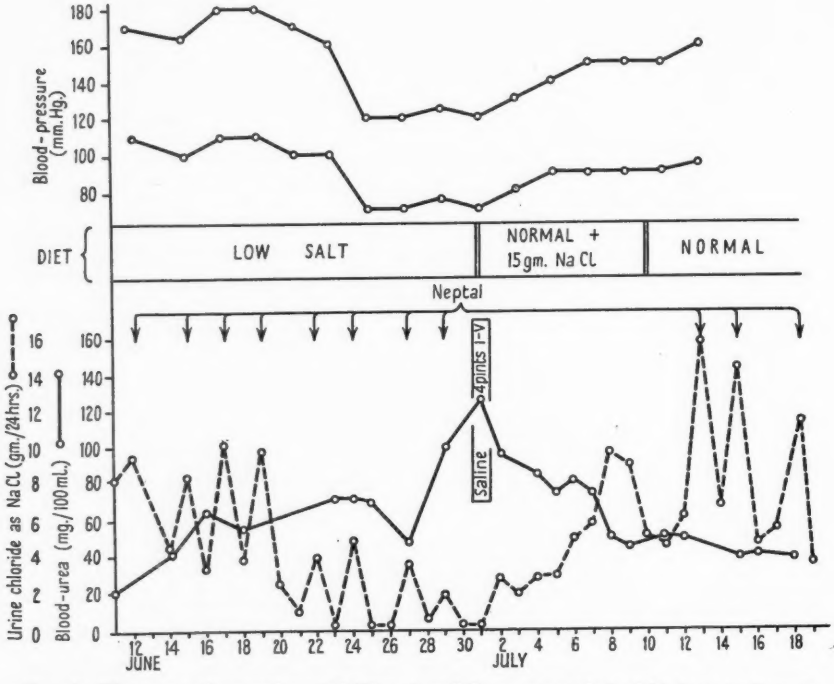

FIG. 3. The same observations (cf. Figs. 1 and 2) over a period of 39 days in Case 8.

urea reached 90 mg. per 100 ml., four pints of physiological saline were given intravenously, and a normal diet was resumed. The blood-urea, blood-pressure, and urinary chloride output returned promptly to normal. As in Case 6, there was no visible oedema throughout the period under discussion. Fig. 3 shows the observations in Case 8. After 18 days on a low salt diet and eight injections of neptal, about five days after the disappearance of oedema, salt excretion practically ceased. It was then found that the blood-urea had risen to 125 mg. per 100 ml., and the blood-pressure, originally 170/110, was now only 110/70. Four pints of physiological saline were given intravenously, and a normal diet with 15 gm. of added sodium chloride was substituted for the low salt diet. Within a week the blood-pressure rose to 150/80 and the blood-urea and urinary chloride excretion returned to normal. There was no return of oedema.

Renal function studies. To obtain further information of the effect of salt-depletion on renal function, the glomerular filtration rate and renal plasma-flow were determined by the technique of Goldring and Chasis (1944), using inulin and diodone respectively. Urea clearances were determined at the same time.

During each period three consecutive determinations were made. The results and mean values are shown in Tables III and IV. Table III shows the observa-

TABLE III

Inulin, Diodone, and Urea Clearances in Case 7

Period 1, severe salt-depletion; period 2, after recovery; period 3, second period of salt-depletion; period 4, half an hour after saline infusion.

Period	*Date and time*	*Blood-urea (mg./100 ml.)*	*Clearances (ml./min.)*		
			Inulin	*Diodone*	*Urea*
1	*17.3.49*	215			
	10.00–10.15		6·1	29·7	1·9
	10.15–10.30		8·4	43·1	2·7
	10.30–10.45		8·1	39·2	2·7
	Mean		7·5	37·3	2·4
2	*4.4.49*	40			
	10.00–10.15		53·8	360	30·3
	10.15–10.30		52·3	354	26·2
	10.30–10.45		49·6	358	24·9
	Mean		51·9	357	27·1
3	*14.4.49*	90			
	10.00–10.15		36·3	306	18·3
	10.15–10.30		29·8	267	15·1
	10.30–10.45		27·3	220	10·5
	Mean		31·1	264	14·6
4	*14.4.49*	90			
	11.40–11.50		44·6	364	23·2
	11.50–12.00		44·6	307	18·4
	12.00–12.10		48·5	410	22·5
	Mean		45·9	360	21·3

TABLE IV

Inulin, Diodone, and Urea Clearances before and after Rapid Saline Infusion in three Control Cases

W.D. and R.J. were normal men; A.M. was a man aged 50 years with chronic nephritis.

Patient	*Blood-urea (mg./100 ml.)*	*Clearances*					
		Before intravenous saline (ml./min.)			*After intravenous saline (ml./min.)*		
		Inulin	*Diodone*	*Urea*	*Inulin*	*Diodone*	*Urea*
W.D.	18	99	1,184	82	106	1,069	77
		111	1,243	80	94	919	63
		113	1,209	79	100	904	65
	Mean	107	1,211	80	100	965	68
R.J.	27	114	328	69	93	413	73
		115	452	74	77	359	68
		117	519	72	103	425	78
	Mean	115	433	72	91	399	73
A.M.	210	10	27	4	11	19	4
		7	22	3	13	18	4
		7	19	3	10	18	5
	Mean	8	23	3	11	18	4

tions in Case 7. Period 1 (March 17, 1949) was during severe salt-depletion and uraemia, period 2 (April 4, 1949) after recovery therefrom, and period 3 (April 14, 1949) during a second period of salt-depletion. Immediately after period 3, four pints of physiological saline were given intravenously in 40 minutes, and 30 minutes after the end of the infusion the measurements of period 4 were made. The greatly depressed renal function of period 1 was followed by a return towards normal of the clearance figures after the uraemia had been abolished (period 2). The rapid intravenous infusion of saline in this type of uraemia affected renal function surprisingly rapidly, since improvement was obvious even half an hour after the infusion (periods 3 and 4). That uraemia was due to salt-depletion is strongly suggested by the failure of control cases to show a similar alteration in renal function after the intravenous administration of the same amount of saline (four pints in 40 minutes) (Table IV). Three control cases are shown, W.D. and R.J. being normal adult men, while the patient A.M. was suffering from a degree of uraemia comparable to that of Case 7, but due to chronic nephritis without salt-depletion.

Discussion

Reasons have been given, based on examination of the kidneys of the patients who died and on estimation of the urinary protein and casts excreted daily by those who recovered, for believing that uraemia in these cases was not due to renal structural damage. We have found in the literature only two cases in which death from uraemia was attributed to renal damage from mercurial diuretics. In one (Cabot series 31451, 1945) the patient had acute glomerulonephritis with anuria before the mercurial was given. In the second case (Waife and Pratt, 1946) the published microphotograph showed changes which would seem insufficient to cause uraemia. The dangers of salt-depletion uraemia have been described by Poll and Stern (1936), Klinghoffer (1941), Soloff and Zatuchni (1949) and Weston, Grossman, Escher, Mokotoff, and Leiter (1950). Our eight cases of uraemia, of which five were fatal, occurred between May 1948 and July 1949 among 62 patients with congestive heart failure treated by injections of neptal and a low sodium diet. The dangers of salt-depletion during the use of this form of treatment therefore deserve wider recognition. It is, of course, well known that salt-depletion even in healthy subjects (McCance, 1936 *a*, *b*) may produce symptoms similar to those experienced by our uraemic patients, and that these symptoms are accompanied by a raised blood-urea. In heat exhaustion (Ladell, Waterlow, and Hudson, 1944) diabetic ketosis, Addison's disease, and pyloric stenosis, and as a sequel of repeated gastric aspiration (Nicol, 1940) the plasma volume is reduced, and salt-depletion, high blood-urea levels, and hypotension are present. It is not surprising that severe restriction of salt intake, together with an excretion of salt augmented by mercurial injections, should lead to salt-depletion, reduction of extracellular fluid, hypotension, a fall in renal blood-flow and glomerular filtration rate, and uraemia. It is surprising, however, that these effects should occur in patients with heart failure within

a very few days of the disappearance of oedema, and even as in Case 5, while oedema is still present.

Conclusion

In many cases of congestive failure it seems unfortunately to be necessary to produce a degree of salt-depletion in order to reduce venous congestion and to abolish oedema. One of the ways, perhaps the chief way, in which the mercurial diuretics act is by promoting renal excretion of salt. The water diuresis is possibly a secondary response mediated by the 'osmo-receptor' and the posterior pituitary. If a reduction of dietary sodium is also enforced, salt-depletion is rapidly achieved, often leading to the prompt disappearance of oedema and venous congestion. Occasionally salt-depletion goes too far and, even while oedema is still present or has barely disappeared, may lead to a rapidly rising blood-urea and death in uraemia. It is suggested that patients who are receiving injections of mercurial diuretics for heart failure should not be placed on a low sodium diet unless it proves impossible otherwise to dispel oedema. When a low salt diet is introduced the blood-urea should be estimated daily or on alternate days. If it rises materially, the low sodium diet should be replaced by one containing a normal amount of sodium. If uraemic symptoms develop the patient should immediately be given at least three pints of twice-normal saline intravenously, and in addition 15 gm. of sodium chloride daily by mouth, until the daily salt excretion returns to a normal level of five to six grammes.

Acknowledgements

We are indebted to Dr. Oscar Brenner for his help and advice in the preparation of this paper. We also thank Dr. R. Gaddie and Dr. M. J. Meynell for their assistance.

APPENDIX

Case Reports

Case 1. W.S., a man of 68 years, was admitted to hospital on May 4, 1948, suffering from hypertensive cardiac failure. He was dyspnoeic at rest and orthopnoeic, and had considerable sacral oedema. The urine contained no albumin and no microscopic deposit. The urea clearance was 29 per cent. of normal, the urea concentration reached only 0·70 gm. per 100 ml., and the blood-urea was 80 mg. per 100 ml. Treatment was begun with rest in bed, digitalis, low salt diet, and injections of neptal. After the sixth injection, on the 15th day after admission, he became strange in his manner, and developed a fine purpuric rash across the shoulders. The injections were stopped, and four days later the blood-urea was found to be 320 mg. per 100 ml. It continued to rise, and in five days reached 440 mg. per 100 ml., shortly before his death. Three days before death the urinary chloride concentration was 0·6 gm. per litre. The patient died on his 26th day in hospital with the clinical and biochemical manifestations of uraemia. At autopsy there were small pleural and pericardial effusions. The heart weighed 600 gm., and showed gross left ventricular hypertrophy. The myocardium showed diffuse fine fibrosis, the valves were normal, and the coronary arteries showed only mild atheroma. The liver and spleen showed chronic venous congestion, and the kidneys showed advanced arteriosclerotic contraction.

Case 2. J.R., a man aged 73 years, was admitted to hospital on May 11, 1948, suffering from congestive cardiac failure secondary to coronary arterial disease, with a history suggestive of a coronary occlusion two months previously. He was dyspnoeic at rest and orthopnoeic, and there was oedema of the ankles and sacral region. The urine contained no albumin and no abnormal microscopic deposit. The urinary urea concentration reached 2·45 gm. per 100 ml., and the blood-urea was 45 mg. per 100 ml. Treatment was commenced at once with rest in bed, digitalis, low salt diet, and intravenous injections of neptal. On the sixth day, after only three injections of neptal, he became mentally confused, and it was found that the blood-urea had risen to 152 mg. per 100 ml.; its level fluctuated considerably for about a month, and then returned to normal. A further trial dose of neptal, 0·5 ml. of a different batch, was given intravenously on the 43rd day, but two hours after this injection an attack of ventricular tachycardia developed, and was confirmed by an electrocardiogram. This attack was terminated by the administration of quinidine, and a further electrocardiogram the following day showed evidence of a recent myocardial infarction, presumably the cause of the attack. Five days after the injection of neptal the blood-urea rose to 118 mg. per 100 ml., but before death occurred from congestive failure on the 61st day it had fallen to 78 mg. per 100 ml. Autopsy showed a recent mycocardial infarction at the apex of the left ventricle, and an older infarct adjacent to it. The viscera showed chronic venous congestion, and apart from this the kidneys were macroscopically normal.

Case 3. E.B., a woman aged 69 years, was admitted to hospital on May 21, 1948, suffering from congestive cardiac failure, which was secondary to essential hypertension and coronary artery disease with angina pectoris. She was dyspnoeic at rest and severely orthopnoeic. There was marked oedema of the legs and sacral region. The urine contained only a trace of albumin and an occasional granular cast. The urea clearance was 46 per cent. of normal, and the urea concentration reached 1·70 gm. per 100 ml. The blood-urea was 58 mg. per 100 ml. She was treated with rest in bed, digitalis, low salt diet, and injections of neptal. After two injections, each of 2 ml., the blood-urea was found to have risen to 80 mg. per 100 ml., and a week later it was 110 mg. per 100 ml. No further injections of neptal were given, and the blood-urea fell after two weeks to its original level. She was discharged to a convalescent home at the end of six weeks, with the recommendation to continue with digitalis and a low salt diet. She was readmitted to hospital on August 14, 1948, with a severe recurrence of congestive failure. The urine still contained only a trace of albumin, occasional hyaline casts, and scanty degenerate red blood-cells. The blood-urea was 67 mg. per 100 ml. The following day she received a test dose of 5 ml. of the dilute preparation of neptal intravenously, and after a week the blood-urea had risen to 180 mg. per 100 ml. It continued at this level for about 16 days and then gradually fell to 47 mg. per 100 ml. just before her death from congestive failure on the 35th day in hospital. It is of some interest that between the seventh and twelfth days she received injections of dimercaptopropanol (BAL) without improvement. Autopsy showed chronic venous congestion of the viscera, and an old myocardial infarction at the apex of the left ventricle. The kidneys showed only arteriosclerotic contraction.

Case 4. G.D., a man aged 62 years, was admitted to hospital on May 31, 1948, on account of congestive failure secondary to hypertension. He was dyspnoeic and orthopnoeic, and there was marked oedema of the ankles and sacrum, ascites, and a small right pleural effusion. The urine showed a cloud of albumin and scanty granular, hyaline, and epithelial casts. The urea clearance was

64 per cent. of normal, and the urea concentration rose to 2·3 gm. per 100 ml. The blood-urea was 20 mg. per 100 ml. He was treated with rest in bed, digitalis, and a low salt diet. After one injection of 2 ml. neptal intravenously he became drowsy, and the blood-urea rose to 118 mg. per 100 ml.; after two weeks it returned gradually to normal. The low salt diet was discontinued, and further injections of neptal were given; these did not affect the blood-urea, but purpuric skin rashes were produced, and the injections were therefore discontinued. He was sent home after six weeks free from signs of congestive failure, with a blood-urea of 50 mg. per 100 ml., and with the recommendation to continue digitalis and a low salt diet. After a month he was readmitted with a recurrence of congestive failure. On this occasion he was treated with a diet without added salt (approximately 5 gm. sodium per day) and intramuscular injections of mersalyl, without adverse effects. It has since been learned that he died at home about six months later of congestive cardiac failure.

Case 5. T.M., a man aged 56 years, was admitted to hospital on September 6, 1948. He had been known to be hypertensive for four or five years, and four years previously had been in hospital for congestive failure. For six weeks prior to the present admission he had been dyspnoeic and orthopnoeic. During these weeks he had been taking digitalis, and had been given three intramuscular injections of mersalyl. On admission he was dyspnoeic at rest and orthopnoeic, and there was gross oedema of the legs, genitalia, and sacral region, with ascites and a small right pleural effusion. The urine contained a cloud of albumin, with a few hyaline, epithelial, and granular casts. The urea clearance was 96 per cent. of normal, and the urea concentration rose to 2·65 gm. per 100 ml. The blood-urea was 58 mg. per 100 ml. Treatment was begun with rest in bed, digitalis, and a low salt diet. After four intramuscular injections of neptal, 18 days after admission, the blood-urea was found to have risen to 136 mg. per 100 ml., and the blood-chloride was only 435 mg. per 100 ml. (as NaCl). The blood-urea continued to rise, and on the 22nd day was 304 mg. per 100 ml. Intravenous physiological saline was administered, but death occurred on the 24th day. Just before death the blood-chloride was 480 mg. per 100 ml. and the blood-urea 210 mg. per 100 ml. At autopsy there was still marked oedema of the lower part of the body, with ascites, pleural and pericardial effusions, and chronic venous congestion of the viscera. The kidneys showed only mild arteriosclerotic changes.

Case 6. A.J., a man aged 71 years, was admitted to hospital on February 28, 1949, suffering from hypertensive cardiac failure. He had been short of breath on exertion for about a year, and had experienced orthopnoea and swelling of the ankles for about a month. He was dyspnoeic at rest and orthopnoeic, and had oedema of the legs and sacral region. The urine occasionally contained a trace of albumin and scanty hyaline and granular casts. The urea concentration rose to 2·60 gm. per 100 ml. The serum-chloride was 630 mg. per 100 ml. (as NaCl). He was treated with rest in bed, digitalis, low salt diet with unrestricted fluids, and intramuscular injections of 2 ml. neptal on alternate days. Visible oedema disappeared within a week of admission. The biochemical observations have been shown in Fig. 1. On March 10, 10 days after treatment was started, he vomited and complained of thirst, although the blood-urea had not risen. Neptal was stopped the next day, but two days later he complained in addition of orthostatic faintness, drowsiness, lassitude, nausea, and anorexia. The blood-urea had risen to 130 mg. per 100 ml. After another two days the blood-urea had risen to the alarming height of 215 mg. per 100 ml., and the serum-chloride was 570 mg. per 100 ml. Since there were good grounds for thinking that his

condition was the result of salt-depletion, three pints of physiological saline were given intravenously that evening. By midnight there was considerable subjective improvement. The blood-urea had fallen to 160 mg. per 100 ml., and the serum-chloride had risen to 640 mg. per 100 ml. This improvement was maintained, and the blood-urea continued to fall rapidly. During the next three days 15 gm. of sodium chloride were given daily by mouth in addition to his diet. His clinical condition improved as the urinary chloride output and the blood-urea returned to normal levels, which were maintained for a week while a normal diet was allowed. There was no return of oedema. On March 21 a low salt diet was resumed, with further injections of neptal. After five days the urinary chloride excretion had fallen to 0·2 gm. in 24 hours, and the blood-urea had risen from 48 to 78 mg. per 100 ml.; the serum-chloride was 575 mg. per 100 ml. As the patient's clinical condition was not giving rise to anxiety no intravenous saline was administered, but a normal diet was substituted for the low salt diet, and injections of neptal were withheld for the next 12 days. During this time the urinary chloride output rose to between 5 and 6 gm. in 24 hours, and the blood-urea fell to 39 mg. per 100 ml. An injection of neptal on April 7 produced an anticipated peak in chloride output—17·4 gm. in 24 hours—followed by a period of chloride conservation for two days. He was sent home four days later free of symptoms apart from some breathlessness on exertion, with a blood-urea of 30 mg. per 100 ml., and afterwards remained well with digitalis, a normal diet without added salt, and intramuscular injections of neptal once a week.

Case 7. W.G., a man aged 72 years, was admitted to hospital on February 23, 1949. He was suffering from congestive cardiac failure due to coronary arterial disease with angina pectoris. He was dyspnoeic at rest and orthopnoeic, and had oedema of the legs, back, and genitalia. The urine contained 0·5 gm. of protein per litre and scanty granular casts. The blood-urea was 52 mg. per 100 ml., and the serum-chloride 595 mg. per 100 ml. He was treated with rest in bed, digitalis, low salt diet, unrestricted fluid, and intramuscular injections of 2 ml. neptal on alternate days. There was no visible oedema 10 days after admission. The biochemical observations have been shown in Fig. 2. The period of salt depletion, shown by low urinary chloride output, began on March 12, and was accompanied by uraemia. On this day the patient became mentally confused, and insisted on walking around the ward in the early hours of the morning. He remained confused all day, and on the following day he was drowsy and lethargic. The significance of these symptoms was not fully appreciated, and a further injection of neptal was given next morning. By March 15 the drowsiness and mental confusion were more marked, and the blood-urea was found to be 145 mg. per 100 ml. and the serum-chloride 529 mg. per 100 ml. On March 17 the blood-urea was 165 mg. per 100 ml., and the blood-pressure was 120/70, having been 170/90 before treatment was begun. Four pints of physiological saline were given intravenously, and three pints daily by mouth for the next six days. As the chloride depletion was corrected the blood-urea level returned to normal. There was no return of oedema. On a normal diet the blood-urea level remained normal, in spite of two further injections of neptal. The blood-pressure now remained at about 150/80. On April 6 a low salt diet was reintroduced, and after eight days, with three injections of neptal, a period of salt-depletion and high blood-urea levels recurred. The blood-urea was only allowed to rise to 90 mg. per 100 ml., the serum-chloride falling to 535 mg. per 100 ml., before four pints of physiological saline were given intravenously and a normal diet restored. On this occasion the blood-pressure fell to 110/70 and, as his

condition improved, returned to 150/90. He was sent home on April 20, 1949, with a blood-urea of 30 mg. per 100 ml. He continued to take digitalis and a normal diet, but with no salt added as a condiment, and was given 2 ml. of neptal intramuscularly once a week. He was well when we last saw him in April 1950.

Case 8. T.J., a man aged 78 years, was admitted to hospital on June 10, 1949, suffering from hypertensive cardiac failure, and from chronic bronchitis and emphysema. For nine months he had been dyspnoeic on exertion and orthopnoeic, and for three months had noticed oedema of the legs. On admission he was dyspnoeic at rest, with cyanosis and orthopnoea. There was oedema of the legs, genitalia, sacral region, and forearms. The urine contained 0·02 gm. of protein per 100 ml., and microscopically there were only occasional hyaline casts. The urea concentration reached 1·10 gm. per 100 ml., the urea clearance was 44 per cent. of normal, the blood-urea was 42 mg. per 100 ml., and the serum-chloride 610 mg. per 100 ml. A low salt diet was instituted, with digitalis and intramuscular injections of 2 ml. neptal on alternate days, and unrestricted fluids. The daily loss of protein in the urine steadily diminished during treatment, and finally ceased. Oedema disappeared by the 14th day. The biochemical observations have been shown in Fig. 3. On the 18th day, when the urinary excretion of chloride had practically ceased, the blood-urea was 100 mg. per 100 ml., and the blood-pressure had fallen from 170/110 to 110/70. The patient was now very confused, and unaware that he was in hospital. Two days later the blood-urea was 125 mg. per 100 ml. Four pints of physiological saline were given intravenously, the low salt diet was withdrawn and a normal diet substituted, and in addition 15 gm. of sodium chloride were given daily by mouth for nine days. During this period the mental confusion slowly disappeared, the blood-pressure returned to 150/100, the urinary chloride excretion rose to 5 to 6 gm. in 24 hours, and the blood-urea fell to about 40 mg. per 100 ml. There was no recurrence of oedema. Subsequently, with a normal diet, further injections of neptal were given without adverse effect, and the patient was sent home on July 20, 1949. He continued to take digitalis and a normal diet, and received injections of 2 ml. neptal once a week. When last seen in the out-patient clinic in December 1949 he was breathless only on exertion, and had no objective signs of heart failure.

Summary

Eight cases are reported, including five fatalities, in which uraemia developed during the treatment of congestive cardiac failure with a low sodium diet (0·2 gm. per day) and frequent injections of a mercurial diuretic. Evidence is presented that this complication is the result of salt-depletion rather than of mercurial damage to the kidney. The premonitory symptoms and signs of the condition are described, and treatment suggested for its relief.

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HEART FAILURE IN ACUTE NEPHRITIS[1]

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THE occurrence of congestive heart failure in the course of acute nephritis has long been recognized (Goodhart, 1879), the observed frequency of the complication varying from 20 per cent. (Ellis, 1936) to 71 per cent. (Whitehill, Longcope, and Williams, 1939). Its features vary from simple elevation of the jugular venous pressure and oedema to a florid clinical picture with pulmonary congestion, cardiac enlargement, and dyspnoea. The present paper reports observations concerning five patients suffering from acute diffuse glomerulonephritis (Ellis Type 1) in whom heart failure, as evidenced by increased jugular venous pressure, was present on their admission to hospital. The cardiac output and right auricular pressure were measured by means of the cardiac catheter, using the methods of McMichael and Sharpey-Schafer (1944). In three of the patients the relation between body-weight, fluid balance, venous pressure, and blood-pressure was recorded in detail. The study was undertaken in the hope of elucidating to some extent the mechanism of heart failure in acute nephritis.

Case Reports

Case 1. A married woman aged 30 years was admitted to hospital on April 7, 1950, complaining of headache and oedema of the legs and face, which had been present for one week. She had suffered an attack of tonsillitis one month previously. There was no past history of renal disease. She did not complain of dyspnoea, cough, or orthopnoea. On examination there was oedema of the face, back, and legs, and there were a few râles at the lung bases. The pulse was regular, and the pulse-rate 78. The blood-pressure was 150/95 mm.Hg. The jugular venous pressure was raised, and there was tenderness over the liver, which was enlarged. The urine contained a large amount of albumin, with many red blood-cells, leucocytes, and casts; its specific gravity was 1,020. The blood urea was 36 mg. per 100 ml.

Progress (Fig. 1). With diuresis the patient's weight fell, and oedema and jugular venous congestion disappeared. The haematocrit value, which was 30 per cent. on admission, rose to 40 per cent. on the 14th day in hospital.

Case 2. A girl of 15 years was admitted to hospital on April 30, 1950, giving a history of a sore throat three weeks previously, followed five days before admission by swelling of the face and ankles and oliguria. There was no complaint of dyspnoea. On examination the pulse was regular, and the pulse-rate was 90. The heart was slightly enlarged. The blood-pressure was 150/85 mm. Hg, and the jugular veins were congested. There were a few râles at both lung

[1] Received November 10, 1950.

bases. The urine contained albumin, with many red and white blood-cells, and a few casts; its specific gravity was 1,022. The blood urea was 40 mg. per 100 ml. The haematocrit value was 36 per cent.

Progress (Fig. 2). With diuresis the weight and venous pressure fell, and

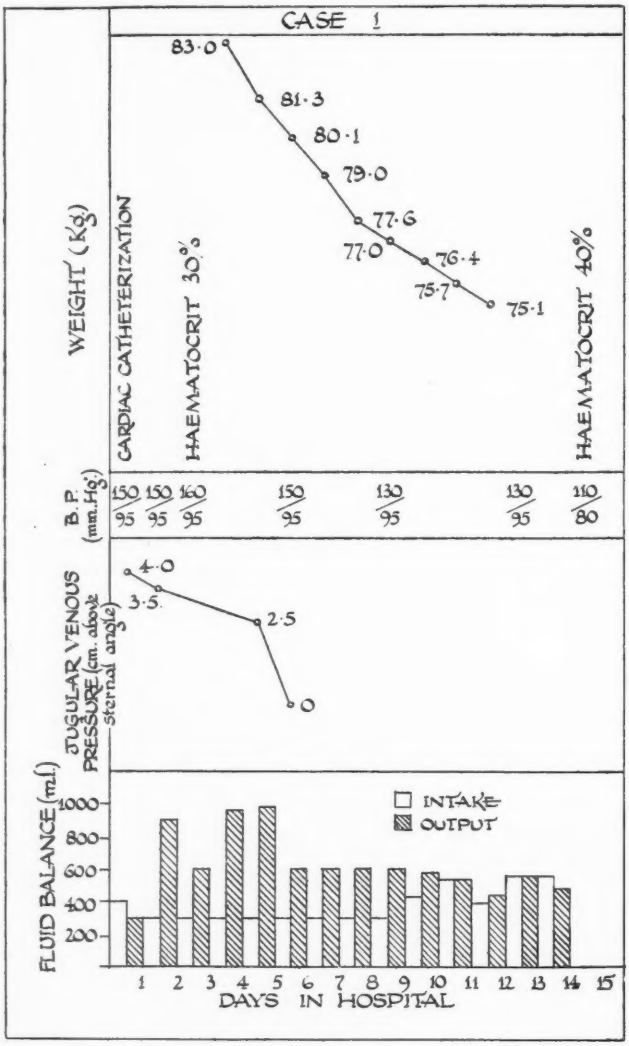

FIG. 1.

oedema disappeared. The patient developed convulsions, associated with a rise of blood-pressure, during the third and fourth days in hospital; there was no concomitant rise of venous pressure. By the 10th day in hospital the haematocrit value had risen to 41·5 per cent., and the blood-pressure had fallen to 110/75 mm.Hg.

Case 3. A man of 26 years was admitted to the ward on June 9, 1950. He gave a history of sore throat followed by otorrhoea three weeks previously, of swelling of the face for five days, and of oedema of the ankles for three days. He had noticed an abrupt decrease in urine output. The patient did not complain of

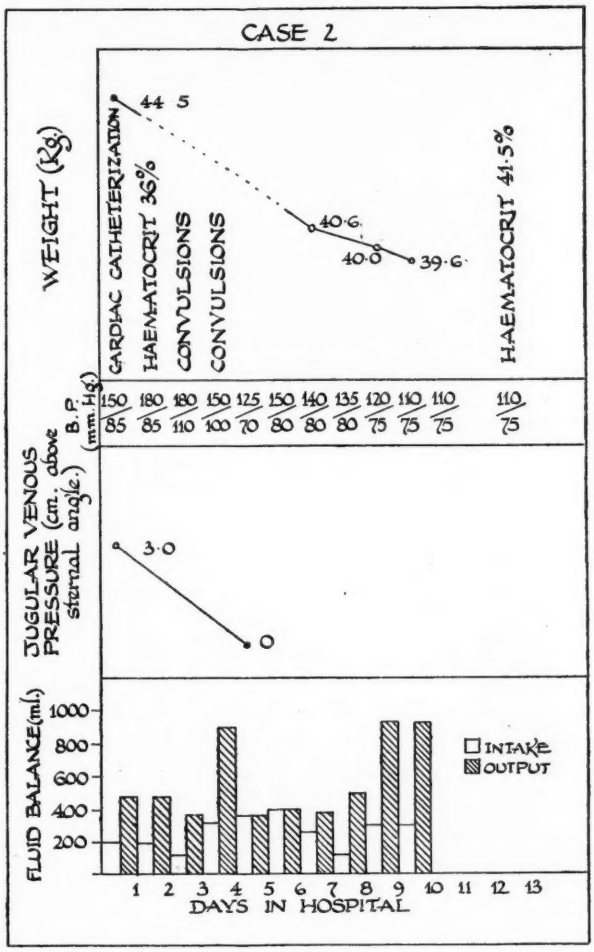

FIG. 2.

dyspnoea. On examination there was moderate oedema of the feet and over the sacrum. The jugular venous pressure was raised, there was slight cardiac enlargement, and the liver edge was palpable. There were no pulmonary râles. The pulse was regular, and the pulse-rate 58. The blood-pressure was 165/95 mm.Hg. The urine contained albumin, red and white blood-cells, and granular and hyaline casts; its specific gravity was 1,018. The haematocrit value was 37 per cent. The blood urea was 58 mg. per 100 ml.

Progress (Fig. 3). Diuresis occurred on the days following his admission to hospital. There was a simultaneous reduction of body-weight and of venous

pressure. The blood-pressure fell to 135/90 mm.Hg. The haematocrit value rose to 41 per cent. on the seventh day in hospital.

Case 4. A housewife aged 25 years was admitted to hospital on November 25, 1948. She gave a history of tonsillitis three weeks before admission; this was

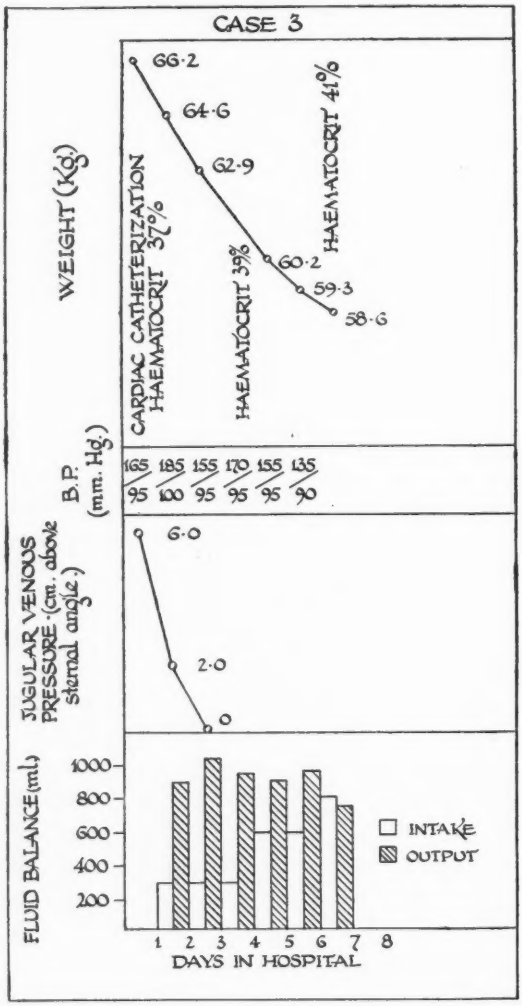

FIG. 3.

followed by oedema of the face seven days before admission, and later by oedema of the legs and hands. There was oliguria. The patient had not noticed dyspnoea. Examination revealed generalized oedema, jugular venous congestion, and slight pulmonary oedema. The pulse-rate was 82, and the blood-pressure 180/100 mm.Hg. The urine contained a large amount of albumin, many

casts, and red and white blood-cells. Its specific gravity was 1,022. The haematocrit value was 36 per cent., and the blood urea 35 mg. per 100 ml.

Progress. Diuresis was associated with a fall of venous pressure and of blood-pressure, and the disappearance of oedema.

Case 5. A man of 42 years was admitted to hospital on January 21, 1950, complaining of oedema of the legs and dyspnoea, which had been present for 10 days; he had suffered a sore throat 14 days before the onset of the illness. On examination he was orthopnoeic; there was oedema of the legs and back,

TABLE

Case number	*Sex*	*Age (years)*	*Pulse-rate per minute*	*Blood-pressure (mm.Hg.)*	*R.A.P. (cm. of saline)*	*Height of R.A.P. above normal*	*R.V.P. (cm. of saline)*	*Cardiac output (litres per minute)*	*Day in hospital at time of observation*
1	F	30	78	150/95	+4·0	9·0	+16·5	5·0	1st
2	F	15	90	150/85	+3·0	8·0	..	5·1	1st
3	M	26	58	165/95	+6	11·0	+21·0	5·8	1st
4	F	25	82	120/70	−1·5	3·5	..	7·4	4th
5	M	42	62	145/85	−2·5	2·5	..	6·0	10th

R.A.P. = Right auricular pressure in relation to sternal angle (normal = −5·0)
R.V.P. = Right ventricular pressure in relation to sternal angle (normal = +5·0)
All pressures are mean values.

and there were râles at the lung bases. The pulse was regular, and the pulse-rate 62. The blood-pressure was 180/105 mm.Hg; the jugular venous pressure was elevated 7·5 cm. above the sternal angle. The urine contained many red blood-cells and casts; its specific gravity was 1,017. The haematocrit value was 33 per cent., and the blood urea 60 mg. per 100 ml.

Progress. Diuresis was associated with a fall of venous pressure and of blood-pressure, and the disappearance of oedema.

Treatment. The diet of all patients was restricted to a small amount of carbohydrate and 300 ml. of salt-free fluids daily until diuresis occurred. None complained of thirst while on this regimen.

Clinical and experimental findings. The results of the observations are recorded in the Table and Figures. They show that the right auricular pressure was raised in all subjects at the time of observation, and that the right ventricular pressure was also raised in the two patients in whom it was measured. In Cases 1, 2, and 3 (Figs. 1, 2, 3) the fall of venous pressure is seen to have been closely associated with diuresis and a fall in weight. Patients 4 and 5 were not weighed frequently, but the fall of venous pressure and the disappearance of oedema were similarly associated with diuresis. All the patients were hypertensive at some stage of their illness, by comparison with the values found in convalescence, but in none was the elevation of blood-pressure great. It can be seen from the Figures that in Cases 1, 2, and 3 the fall of venous pressure preceded any fall of blood-pressure, and in Cases 2 and 3 there was a *rise* of blood-pressure while the venous pressure was falling. Only one patient (Case 5) complained of dyspnoea. The cardiac output at rest was found to be within the normal range in all five subjects, with pulse-rates varying from 58 to 90; hence the stroke output was also normal.

The haematocrit value was low in all patients on initial examination, and in Cases 1, 2, and 3, in whom the estimation was repeated, the value returned towards normal with recovery.

Discussion

Congestive heart failure in acute nephritis has usually been attributed to myocardial damage or to hypertension. The evidence for the existence of myocardial damage is based either on electrocardiographic changes (Master, Jaffe, and Dack, 1937) or on histological examination of the heart in fatal cases (Gore and Saphir, 1948). The electrocardiographic changes which have been recorded are of a minor character, consisting usually of small changes in the T-wave pattern, and La Due (1944) pointed out the poor correlation between these changes and the occurrence of congestive heart failure. Gore and Saphir (1948) examined the hearts of 160 patients who died of acute and subacute nephritis, and in 16 cases they found microscopic evidence of 'myocarditis', consisting of patchy interstitial exudate containing a small number of inflammatory cells; the lesions were few in number and minute in size, and involved only a small part of the heart; the muscle-fibres appeared normal. If myocardial damage were the cause of congestive heart failure, it might be expected that the cardiac output would be low and the pulse-rate rapid; in the subjects of the present investigation the cardiac output was within normal limits, and the pulse was not accelerated. Rubin and Rapoport (1938), among others, put forward the view that heart failure in acute nephritis is the result of hypertension. But Levy (1930) showed that failure may occur without significant hypertension, and Roscoe (1950) observed that diuresis and the diminution of oedema frequently preceded a fall of blood-pressure by several days. In the patients described above only moderate hypertension was present at a time when the right auricular pressure was raised, and it can be seen from Figs. 1 to 3 that the venous pressure was falling while the diastolic blood-pressure remained unchanged or even increased. As a further argument against the hypertensive origin of heart failure in acute nephritis, Master, Jaffe, and Dack (1937) pointed out that the paroxysms of hypertension which occur in patients suffering from pheochromocytoma are not associated with a rise of venous pressure. The finding of a high right ventricular pressure in Case 1 and Case 3 might be regarded as evidence of 'left heart failure' due to hypertension, leading to 'right heart failure', but it has been pointed out above that the disappearance of the signs of 'right heart failure' may precede a fall of blood-pressure. The observation of La Due (1944), that the circulation time in the heart failure of acute nephritis is normal, might be cited as evidence against myocardial damage or hypertension as the causal factor, but the exact significance of the circulation time in heart failure is debatable.

It is suggested that neither of the explanations previously offered is wholly acceptable, and that the following hypothesis might form the basis of further investigations into the genesis of heart failure in acute nephritis. With the onset of the disease the renal circulation is seriously diminished (Black, Platt, Rowlands, and Varley, 1948), and the ability to excrete water and sodium is

impaired. The patient continues to drink in spite of oliguria or anuria, and consequently has a positive water-balance. Some of the retained fluid passes into the tissue spaces to form oedema, while some remains in the vascular tree and raises the venous pressure. Increased venomotor tone may contribute to the rise of venous pressure by reducing the capacity of the vascular bed. This hypothesis finds support from several sources. It was shown by Lyons, Jacobson, and Avery (1944) that the administration of sodium and water to normal subjects in quantities sufficient to overcome their excretory capacity leads to increased weight, increased blood-volume, and a rise of venous pressure. It is, moreover, a commonplace clinical observation that overdosage of desoxycorticosterone acetate may produce cardiac enlargement, pulmonary congestion, increased venous pressure, and oedema, without hypertension, and more recently similar manifestations have occurred as a result of the sodium and water retention induced by cortisone (Carlisle, 1950). It remains to show that there is, in fact, an increase of blood-volume in acute nephritis. Roscoe (1950) pointed out that 'the relation of blood-volume changes to oedema has been investigated by a number of workers, but the earlier work is difficult to interpret, as it is not usually clear to what type of nephritis, or to what stage of the disease, the investigations refer'. MacArthur (1942) found that, at the onset of acute haemorrhagic nephritis, haemoglobin and red-cell estimations were low, and that a rise occurred with the onset of diuresis. The same author (1946) showed by the Congo-red method that the plasma-volume fell as urine output increased. In MacArthur's opinion these findings were to be interpreted as meaning that the blood-volume was normal at the time of the first observation, and fell below normal with diuresis. Cardozo (1946) estimated the plasma-volume by the Evans's blue method in five cases of acute nephritis at the onset and after diuresis, and found that a fall in volume occurred in four of the patients. Roscoe (1950) made careful serial studies of haemoglobin, red-cell, haematocrit, and plasma-protein values in a large number of cases of acute nephritis. She found evidence of increased plasma-volume in the oedematous phase, followed by a decrease when diuresis occurred. In one patient the inferences made from these values regarding plasma-volume were checked by the Evans's blue method, and the correlation was found to be good. The few observations of haematocrit values reported above are in keeping with the findings of Roscoe and MacArthur. La Due (1944), writing of heart failure in acute nephritis, stated: 'Our patients had a prompt diuresis when their heart failure began to clear.' It seems that this proposition could equally well be stated the opposite way, namely that when diuresis occurs the body-water decreases, the blood-volume diminishes, and the features of heart failure disappear.

It is realized that the above hypothesis, while consonant with the evidence supporting the renal origin of venous congestion and oedema in 'low output' heart failure (Merrill, 1946) and in 'high output' heart failure (Davies and Kilpatrick, 1951), is not conclusively proved, and leaves many questions unanswered. The observations of cardiac output were made only at rest, and there is no evidence of the ability of the heart to increase its output in response to

exercise. The mechanisms producing cardiac enlargement and high right ventricular pressure require elucidation. It seems possible that pulmonary hypertension causes dilatation of the right heart, although much higher pressures may be found, e.g. in mitral stenosis, without evidence of congestive heart failure or of cardiac enlargement. Intravascular fluid retention may be an alternative, or accessory, factor in cardiac enlargement. This view may be supported by La Due's observation (1944) of the close correlation between diuresis and diminution in the size of the heart in patients suffering from acute nephritis. The rise of right ventricular pressure observed in Cases 1 and 3 must have been due to increased resistance in the pulmonary vascular bed, since the cardiac output was normal. It seems possible that the mechanism producing vasoconstriction in the systemic circulation in acute nephritis causes similar constriction in the pulmonary arterioles, or alternatively that the increased blood-volume distends the capillary bed in the lungs, and that this process in some way increases resistance.

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Summary and Conclusions

1. Five cases of acute diffuse glomerulonephritis (Ellis Type 1) with raised venous pressure have been studied by cardiac catheterization. The cardiac output and stroke output were within normal limits.

2. In three of the cases detailed records of the blood-pressure, body-weight, fluid balance, and venous pressure were made. These records indicate that the disappearance of the signs of 'heart failure' was directly related to diuresis, and not to a fall of blood-pressure.

3. The evidence for the views that congestive heart failure in acute nephritis is due to myocardial damage, or to hypertension, is not convincing for the following reasons: (*a*) dyspnoea may be absent; (*b*) the cardiac output and circulation time are within normal limits; (*c*) the heart-rate may be normal, or even slow, in the presence of raised venous pressure; (*d*) the correlation between changes in the electrocardiogram and venous congestion is poor, and the histological changes in the myocardium are minimal; (*e*) the correlation between hypertension and venous congestion is poor, and a fall of venous pressure and the disappearance of oedema may precede a fall of blood-pressure.

4. It is suggested that the term 'heart failure' in acute nephritis is misleading in that it directs attention to the heart as the cause of venous congestion, and that the raised venous pressure, oedema, cardiac enlargement, and pulmonary oedema may be attributable to water-retention by damaged kidneys, leading to hydraemia. Increased venomotor tone may be an important contributory factor in raising the venous pressure. It is realized that the evidence adduced for this hypothesis is incomplete.

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CARCINOMA OF THE BRONCHUS[1]

A clinical and pathological survey of 866 cases

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With Plate 20

During the last 30 years primary carcinoma of the lung has been a subject of interest both to clinicians and to pathologists, owing to the increasing frequency with which the disease has been diagnosed and the controversial question whether there has been an apparent or a real increase in its incidence. The recent advances in thoracic surgical technique, and the opportunity it occasionally offers for the radical removal of a primary bronchial carcinoma, have made the early diagnosis of the condition of fundamental importance. In spite of improvements in thoracic surgery and in diagnostic procedures the prognosis in most cases remains hopeless, largely because the patients first seek treatment when the disease has reached an advanced state. The present paper is a clinical and pathological survey of 866 cases of carcinoma of the bronchus, in all of which necropsy was performed by members of the staff of the London County Council Central Histological Laboratory. In every case included in the survey histological examination had been made of the material obtained at necropsy, and in most cases complete autopsy records were available. The clinical notes were gathered from 26 hospitals formerly under the control of the London County Council and situated in the Greater London area. In most cases the clinical records were complete, but in a few, owing to war damage to the hospitals concerned, some of the relevant papers had been destroyed. The investigation was spread over the years 1936 to 1947 inclusive, during which the laboratory staff was almost unchanged and the technique of necropsy remained unaltered. No previous survey of such scope has been attempted in the London area, with the exception of a review of 300 cases undertaken by Barnard in 1938. During the period 1936–47 increasing attention was being paid to the problem of bronchial carcinoma, and as a consequence more patients were sent to thoracic surgical units for treatment. Owing to the intervention of the war some of these units were working at reduced capacity, and a few were forced to close, whereas all the hospitals which supplied records for the present

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survey were non-teaching institutions obliged to accept patients suffering from any non-infective illness, and many of the patients had been transferred from teaching hospitals. Thus the possibility of error due to selection of clinical material was slight, and the results should be fairly representative of the incidence of the disease in the County of London.

The literature dealing with bronchial carcinoma, which has attained enormous proportions, shows conflicting opinions as to whether there is a real or an apparent increase in the incidence of the disease (Rolleston and Trevor, 1903;

TABLE I

Analysis of Post-mortem Figures for the Years 1936–8 and 1945–7

	Post-mortem examinations		
Year	*Total*	*Cases of malignant disease*	*Cases of malignant disease* (%)
1936	684	100	14·6
1937	865	154	17·8
1938	1,075	252	23·4
1945	1,216	335	27·5
1946	1,490	376	25·2
1947	1,723	483	28·0

TABLE II

The Commoner Sites of Malignant Neoplasm expressed as a Percentage of the Total (Post-mortem Figures)

	Year					
Site	*1936*	*1937*	*1938*	*1945*	*1946*	*1947*
Bronchus	25	28·6	22·2	27·3	28·2	27·1
Stomach	10·0	9·7	11·9	10·4	11·7	12·6
Large intestine	5·0	8·4	9·5	11·6	12·8	13·0
Prostate	5·0	5·2	2·7	5·3	3·2	4·1
Kidney	7·0	1·3	2·7	5·3	3·2	4·1

Adler, 1912; Playfair and Wakeley, 1923–4; Duguid, 1927; Bonser, 1928–9; Dunn and White, 1928; Passey and Holmes, 1935; Kennaway and Kennaway, 1936; Fried, 1925, 1927; Jaffé, 1934–5; Frissell and Knox, 1937; Seyfarth, 1924; Katz, 1927; Berblinger, 1925; Kikuth, 1925). Owing to the intervention of the second world war during the period covered by our review, considerable inaccuracies would have been introduced in an attempt to show whether the incidence of bronchial carcinoma was increasing. It was therefore decided to carry out a straddle survey, using the total figures for the disease in 1936, 1937, and 1938, and comparing them with those for 1945, 1946, and 1947. Such a sampling, omitting the war years, should show any tendency towards change in the incidence of the disease. All other data are based upon the total number of cases during the entire period under review. Tables I and II show the number of necropsies performed on patients who died of malignant disease, and the proportions of these deaths attributable to carcinoma of the bronchus, stomach, large intestine, and prostate. The three latter sites are included for comparison

because they were found, in that order of frequency, to be the commonest sites of primary growths after the bronchus. Tumours of such common sites as the uterus, breast, and skin are often diagnosed in the earlier stages and treated by surgery or irradiation; the patients leave hospital temporarily cured and die at home, and this fact would invalidate conclusions as to the true incidence of carcinoma in these sites. It will be seen that the proportion of patients dying of

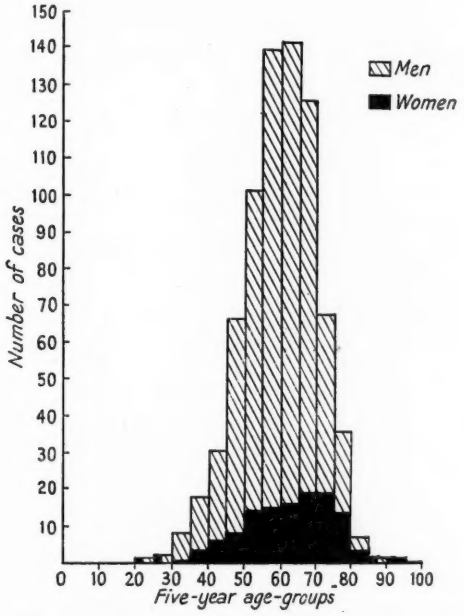

FIG. 1. The incidence of bronchial carcinoma in five-year age-groups and in each sex.

carcinoma of the bronchus over the period of a decade remained nearly constant, in spite of the steadily increasing number of necropsies recorded in all forms of malignant disease. Fig. 1 shows the age and sex incidence of the disease. The average age at which death occurred in both sexes was 59·5 years, but it will be seen from the graph that the peak incidence of the disease in women was at a slightly greater age than in men. The sex ratio of six men to one woman confirms the marked preponderance in men which has previously been a universal finding in this disease (Simons, 1937). In the analysis of occupations (Table III) the low incidence, 7·8 per cent., in transport workers, compared with 16·5 per cent. found by Duguid (1927) in Manchester, is of interest in view of the high concentration of motor transport in the County of London. There is practically no difference in the ratio of outdoor to indoor workers, which in the present series is 1 : 1·3. Unfortunately no figures could be obtained from the case records bearing on the relationship of the habit of smoking to the incidence of the disease, and a plea is made for more careful future recording of the

smoking habits of all hospital patients in the clinical notes. Table IV shows the relationship of previous diseases affecting the chest to carcinoma of the bronchus in both sexes. No history of chronic bronchitis, or of chronic cough, was accepted unless it clearly showed that the complaint was present for many years before

TABLE III

Analysis of Known Occupations

Occupation	*Number*	%
Men		
Labourers	91	20·0
Engineers	44	9·7
Motor vehicle drivers	22	4·9
Transport, other than motor drivers	13	2·9
Building trade	18	4·0
Painters	20	4·3
Outdoor, various	46	10·1
Indoor, various	151	33·1
Dustmen and road sweepers	7	1·6
Stokers	7	1·6
Gasworkers	6	1·3
Asphalt worker	1	0·2
Surface grinder	1	0·2
Marble polisher	1	0·2
Clerks	27	5·9
Total	455	100·0
Women		
Housewives or domestic duties	86	80·4
Various	21	19·6
Total	107	100·0

TABLE IV

Previous Chest Diseases

	Men		*Women*	
Disease	*Number*	%	*Number*	%
Chronic bronchitis and cough	167	22·5	16	13·0
Bronchiectasis	3	0·4	1	0·8
Pleurisy and pneumonia	39	5·2	4	3·3
Pulmonary tuberculosis	13	1·8	..	..
Other chronic lung diseases (pneumokoniosis, &c.)	10	1·3	1	0·8
No previous history of chest disease	511	68·8	101	82·1
Total	743	100·0	123	100·0

the onset of symptoms which were likely to be due to carcinoma of the bronchus. It was found that 29·4 per cent. of all male patients with carcinoma of the bronchus gave a history of long-standing pulmonary disease, excluding pulmonary tuberculosis. The incidence of such pre-existing disease in women was 17·9 per cent., and the difference is statistically significant. The small number of patients (1·8 per cent.) who had active chronic pulmonary tuberculosis, as distinct from microscopical evidence of old chronic tuberculous lesions, confirms the generally accepted view that the association of the two diseases is fortuitous. There were only four examples in the present series of a carcinoma

arising in the wall of a bronchiectatic cavity, but bronchiectasis as a complication of bronchial obstruction due to the carcinoma was exceedingly common.

Symptomatology

Table V shows the chief symptoms in order of frequency in both sexes. The two commonest symptoms, cough and dyspnoea, were of such frequent occurrence in persons of 40 years of age and over that they were disregarded by the

TABLE V

Symptoms and Signs in Order of Frequency

Men (743 cases)		*Women (123 cases)*	
Symptoms	%	*Symptoms*	%
Cough	52·6	Cough	48·8
Loss of weight	35·1	Dyspnoea	35·0
Dyspnoea	33·1	Loss of weight	30·9
Pain in chest	29·6	Pain in chest	28·5
Haemoptysis	26·4	Headache, vertigo, fits, paresis of limbs	19·5
Headache, vertigo, fits, paresis of limbs	14·6	Haemoptysis	8·9
Abdominal pain	9·0	Pain in shoulder	6·5
Pain in back and legs	7·3	Dysphagia	6·5
'Flu'	5·0	Enlargement of lymphatic glands, skin nodules	5·7
Vomiting	3·4	'Flu'	5·7
Pain in shoulder	3·1	Vomiting	4·1
Hoarseness, loss of voice	3·0	Abdominal pain	4·1
Dysphagia	2·8	Medical emergencies	2·4
Enlargement of lymphatic glands, skin nodules	2·7	Hoarseness, loss of voice	0·8
Medical emergencies	1·5		
Jaundice	1·2		

patients, and in many cases they had been present for many years before a marked exacerbation, or additional symptoms, caused medical advice to be sought. Patients frequently gave a history of an acute febrile illness, commonly diagnosed as influenza, which did not improve after a week or two. This history was often associated with the finding of an unresolved bronchopneumonia at necropsy. A further feature of interest was the increased frequency in male patients of haemoptysis, which was usually slight and repeated. It is apparent that, despite the frequency with which the first four symptoms in the Table are encountered in many varieties of thoracic disease, their simultaneous occurrence in any person over 40 years of age should excite suspicion that the patient is suffering from carcinoma of the bronchus, until the existence of that condition has been disproved. The commonest physical signs and symptoms referable to secondary deposits were neurological manifestations, due to metastases in the brain, and gross enlargement of the liver. Such patients frequently first complained of headache, fits, or paresis of limbs, or of increasing size of the abdomen, with or without any signs or symptoms in the chest. In about nine per cent. of all cases the initial symptoms were entirely neurological, and in nearly 15 per cent. neurological symptoms or signs were present in addition to the more usual features of the disease. The great variety of its first manifestations included a

pathological fracture of the mandible, jaundice, and acute medical emergencies such as spontaneous pneumothorax or massive haemoptysis.

Pathology

The distribution of the primary growths in the bronchial tree is shown in Fig. 2. Some of the earlier investigations tended to show a preponderance of

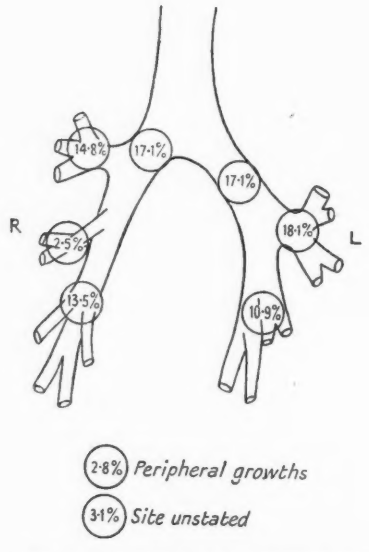

FIG. 2. Diagram showing percentage distribution of primary growths in the bronchial tree.

primary sites in the right lung (Willis, 1948; Simons, 1937). The present series shows an almost equal distribution between the two sides. The small proportion of peripheral neoplasms is noteworthy; tumours arising in the outlying parts of the lung are of special clinical interest, because their presence was usually first indicated by the signs of metastases in other systems, or by the results of pleural irritation. In a few cases, which are not included in the series, an unusually careful examination failed to reveal a primary bronchial growth, but the distribution and histological character of the secondary deposits left little doubt that the bronchus was the primary site. The fact that the primary tumour may be extremely small, and even of microscopic size, is now well recognized, and adds greatly to the difficulties of clinical diagnosis. Five examples of the so-called Pancoast tumour were seen. Four were bronchial carcinomata which had arisen in the apical region of the upper lobe and had directly infiltrated the soft tissues at the root of the neck, and the fifth was due to a secondary deposit in the first rib from a small primary growth situated in a main bronchus. No evidence was found that these 'superior pulmonary sulcus tumours' differed in

any way from other bronchial carcinomata except in the clinical syndrome they produced, which was entirely due to their anatomical situation.

From its point of origin in the bronchus carcinoma may spread by direct infiltration, by lymphatic permeation, or by the blood-stream. The first method of spread may involve the adjacent lung, and a combination of the first and second methods may lead to infiltration of the pericardium, or to pressure on the great vessels entering the hilum of the lung. In growths arising in the posterior and upper part of the lung, direct infiltration of the chest wall and heads of the ribs is sometimes found. In 9·3 per cent. of the present series direct infiltration of mediastinal structures had occurred, and in some cases had caused thrombosis of the great veins of the neck above a point of obstruction in the superior vena cava, and even interference with the venous return to the right side of the heart. A noticeable feature in many cases was a tendency of the growth to spread beneath the mucous membrane of the bronchus without causing surface ulceration or obstruction to the lumen. The second method of spread, by lymphatic permeation, involved both the lungs and the regional glands. Within the lungs the spread was mainly by the perivascular lymphatic channels, and to a very much less extent along the peribronchial lymphatics. The perivascular lymphatic spread was important, because it sometimes appeared radiologically as reticular shadows in the lung fields. Of the more distant groups of glands the lower deep cervical, upper abdominal, and para-aortic lymph-nodes were very frequently involved. The authors' experience since the survey has tended to show that these groups of glands are more often involved than the figures in Table VI indicate. The haematogenous method of spread, owing to the extensive vascular network in the lung and the close relation of the growth to the pulmonary circulation, frequently leads to very early and extensive distant metastases, from which no organ in the body is exempt. Rarely a diffuse form of intracapillary vascular spread within the lung was encountered (Plate 20, Fig. 3), and involvement of the opposite lung was sometimes found if the superior vena cava had been invaded by growth. Table VI shows the distribution of the lymphatic and blood-borne metastases in various organs. The liver was the organ most frequently affected, and after it the adrenal glands and brain, organs which are generally recognized as common sites of metastasis in bronchial carcinoma. Since the skull was opened as a routine procedure at almost all necropsies, the figure shown probably indicates the true frequency of metastatic growth in the brain. The figure of 13·0 per cent. given for skeletal metastases is too low, since it is impossible to examine in detail every bone of the skeleton, and the true incidence is probably very much greater. From a review of all the sites in which metastases were found the conclusion was reached that no organ or site could be considered exempt. The unusual frequency with which the adrenals were involved led to careful examination of these organs, to determine whether metastases reached them by the blood or by secondary lymphatic spread from adjacent upper abdominal glands. Such evidence as was found suggested that spread was by the blood-stream, the carcinoma cells being arrested in the medullary plexus of capillaries. This inference was supported

by the greater frequency with which secondary deposits occurred in the rich capillary plexus found in small cortical adrenal adenomata.

For the purposes of the present survey carcinoma of the bronchus was classified into five main histological types: the group of oat-celled and round-celled growths, the polygonal-celled group, the squamoid and squamous-celled groups, and the adenocarcinomata. No growth was accepted as an example of a

TABLE VI

Distribution of Secondary Growths (Men and Women)

Organ	*Number of cases*	%
Cervical, supraclavicular, and axillary lymph-nodes	77	8·9
Abdominal lymph-nodes	120	13·8
Liver	307	35·4
Adrenals	206	23·8
Brain	148	17·0
Kidney	107	12·4
Heart and pericardium	81	9·3
Pancreas	73	8·4
Skin	31	3·6
Spleen	35	4·0
Thyroid	19	2·2
Other sites (combined)	78	9·0
Skeletal	113	13·0
No secondaries	240	27·7

squamous-celled carcinoma unless many of its constituent cells showed prickles, or keratin was present. If the cells merely resembled squamous cells, without either of the above two features, the tumours were classified as squamoid. As Barnard showed in 1926, carcinoma of the bronchus, like many other varieties of carcinoma, is often characterized by extreme pleomorphism in its histological structure. Two or more of the five types of growth were often present together in different parts of the same tumour. It was repeatedly observed that oat-celled growths tended to remain the most uniform in structure, both in the primary and in the secondary sites, except for areas of spindle-celled metaplasia. Little significant difference was found in the ages at which the different histological types of growth occurred (Table VII). The oat-celled variety accounted for a little over a third of all cases, and occurred at a slightly earlier average age than the other varieties. Table VII also shows the relation of the histological type to the presence or absence of metastases, and shows a greater liability to metastasis in oat-celled, polygonal-celled, and adenocarcinomatous growths than in the more highly differentiated squamoid and squamous-celled varieties. A high degree of malignancy is demonstrated in the group of adenocarcinomata, although such growths have usually been considered to be more highly differentiated and therefore less malignant. More adenocarcinomata occurred in men than in women, a finding which is contrary to that of other workers. Table VIII shows the duration of the first symptoms to the time of admission to hospital, and the expectation of life from the appearance of the first symptoms, in relation to the histological type of growth. Again with the exception of the

squamoid and squamous-celled groups, the prognosis as regards the duration of life from the first recorded symptom was found to be under six months. Although the prognosis remains so appalling in this disease, it is probable that many carcinomata arising in the bronchi are very slow-growing tumours, and only attract attention late in the course of their growth by interfering with lung function. Such a case was that of a man who had been under continual clinical

TABLE VII

Relation of Type of Growth to Frequency of Metastases, and Average Age of Patients (Men and Women)

Type of growth	*Number of cases*	%	*Average age of patients (years)*	*With metastases* %	*Without metastases* %
Oat-celled	312	36	57·2	79·6	20·4
Polygonal-celled	348	40·2	60·3	74·1	25·9
Squamoid	97	11·2	64·3	52·2	47·8
Squamous-celled	60	6·9	60·0		
Adenocarcinoma	42	4·9	63·3	83·3	16·7
Not stated	7	0·8	54·1	..	..
Total	866	100·0	59·5		

TABLE VIII

Duration of First Symptoms and Duration of Life in relation to Histological Type of Growth

	Men			*Women*		
		Average duration in weeks of			*Average duration in weeks of*	
Type of growth	*Number of cases*	*first symptoms before admission to hospital*	*life from beginning of symptoms*	*Number of cases*	*first symptoms before admission to hospital*	*life from beginning of symptoms*
Oat-celled	272	17·2	21·6	41	21·3	25·9
Polygonal-celled	303	19·0	21·2	45	16·0	20·9
Squamoid and squamous-celled	140	27·3	32·3	17	18·9	25·0
Adenocarcinoma	25	18·9	25·1	16	17·1	20·3
Not stated	3	13·3	33·7	4	21·0	26·0
Total	743	19·9	23·5	123	18·3	23·1

and radiological observation after a total gastrectomy performed for carcinoma of the stomach. A routine follow-up examination of the chest by X-rays revealed a shadow in the lower right lung field. This shadow was observed to increase slightly in extent over a period of 15 months, and was regarded as a secondary deposit from the excised tumour of the stomach. Eventually the patient sought hospital treatment, and died a year and a half after the lung shadow was first observed. The tumour in the lung was shown at necropsy to be an independent primary carcinoma of the bronchus. More striking examples of the slow growth of lung tumours were recorded by Fried and Buckley (1930), one of whose patients survived for six years. In view of the slow development to be expected of some growths, we have recently attempted to examine the bronchial tree with great care at all autopsies, but only one unsuspected carcinoma has so far been found.

The recent advances in the technique of thoracic surgery, and the greater number of cases of bronchial carcinoma which have been accepted as suitable for excision, have led to the clinical division of the growths into hilar and peripheral types. Such a division has engendered a false sense of security when dealing with growths arising peripherally because these tumours are usually considered to metastasize more slowly. Although lymphatic spread to the central hilar glands may be delayed, this variety of growth appears to be as liable as the commoner central variety to metastasize early by the blood-stream. It is generally recognized that, in many sites, carcinomata may arise simultaneously at more than one place from a field of epithelial cells which are all capable of undergoing malignant change. In one case in the present series two apparently independent primary growths, a squamous-celled and an oat-celled carcinoma, were found arising in independent bronchi, one in each lung.

Any description of the pathology of carcinoma of the lung inevitably includes mention of the relationship of the tumour to bronchial adenoma, alveolar-celled carcinoma, and pleural endothelioma. In the course of the present survey 11 cases of bronchial adenoma were encountered. It is not proposed to describe further the clinical characteristics and pathology of this group of tumours. Their relationship to carcinoma of the bronchus has always been difficult to prove, but from the small number of cases seen during the period of this survey it seems that the bronchial adenoma tends sooner or later to become a true carcinoma. An example is shown in Plate 20, Figs. 4 and 5, in which a pulmonary growth with the characteristics of the alveolar type of bronchial adenoma gave rise to a metastasis in the kidney having a similar histological structure. Adams, Steiner, and Bloch (1942) described similar malignant changes in a small series of bronchial adenomata, the history in some of their patients having extended back over 15 years. Serial microscopic sections of a small bronchial adenoma, which was recently discovered incidentally at necropsy, suggest that these tumours may arise from the bronchial glands rather than from the surface epithelium. The close resemblance in microscopical structure between the bronchial adenoma and the mixed salivary tumour has been noted by Foster-Carter (1941) and Willis (1948). From our own observation the relation of bronchial adenoma to bronchial carcinoma appears to be much the same as that of a basal-celled cutaneous carcinoma (rodent ulcer) to a squamous-celled carcinoma of the skin. From time to time individual cases of diffuse pulmonary adenocarcinoma, sometimes known as malignant pulmonary adenomatosis and alveolar-celled carcinoma, have been reported in the literature (Dacie and Hoyle, 1942) and two examples of this condition were seen during the present investigation. The macroscopic and microscopic appearances were very striking, for to the naked eye the lung resembled a lobar pneumonia due to a pneumococcus type III infection, the cut surface being solid, grey, and mucoid. Microscopically all the alveoli appeared to be lined with columnar mucus-secreting cells, which in places had invaded the stromal tissue, showing their malignant nature (Plate 20, Fig. 6). The possibility has been suggested that the condition is related to *Jaagsiekte*, or pulmonary adenomatosis of sheep

and dogs. *Jaagsiekte*, however, with one possible exception, has never been known to give rise to metastases outside the lungs, and has usually, though not unanimously, been regarded as an infectious disease (Drymalski, Thompson, and Sweany, 1948). In the course of the authors' survey no evidence was found that carcinoma could arise directly from alveolar lining cells, whose existence in a normal lung still remains unproved, and the diffuse adenomatosis was attributed to down-growths of malignant bronchiolar epithelial cells into the terminal alveoli. Such down-growth of bronchiolar epithelium can be clearly seen in the non-malignant pulmonary adenomatosis of sheep. A few examples of carcinoma of the lung were seen in which a pleural spread had enclosed the lung in a thick casing of growth, which had extended into the interlobar fissures, and had caused obliteration of the pleural sac by a sheath of growth up to one cm. thick. These specimens showed no apparent involvement of the underlying lung, and the growths were often referred to as pleural endotheliomata, though microscopical examination showed that most of them were indistinguishable from acinar, polygonal-celled bronchial carcinomata which had spread at an early stage into the subpleural lymphatic plexus, and thence along the subpleural lymphatic channels as the line of least resistance. Endotheliomata of the pleura probably occur no more frequently than endotheliomata of other serous surfaces such as the peritoneum and pericardium.

Diagnosis and Treatment

In 804 cases the original radiograph of the chest, or a report on such a radiograph, was available, and the accuracy of the initial clinical and radiological diagnoses was compared. The initial error in clinical diagnosis amounted to 50·4 per cent., and in radiological diagnosis to 60·4 per cent. The radiological diagnosis of carcinoma of the bronchus, as usually carried out, is likely to remain uncertain because the primary growth is frequently concealed by secondary pathological changes in the lung, the chief of which are collapse, unresolved bronchopneumonia, and pleural effusion. It is therefore important at present not to place great reliance on a negative radiological report in excluding carcinoma. The survey also showed that a radiological report of an unexplained pleural effusion, lung opacity, or excessive hilar shadowing in any person of middle age should have immediately prompted further investigation, particularly bronchoscopy and examination of the sputum for malignant cells. A survey was made of the results of different methods of treatment in those cases in which the records were available and complete. Of a total of 752 patients only 48 were considered suitable for deep X-ray therapy, and in only six cases was extirpative surgery attempted. These figures further serve to show the late stage at which most of the patients sought treatment. The average duration of life following a full course of irradiation was 51·2 weeks, and in the six patients subjected to surgical extirpation it was 47·5 weeks. The proportion of cases deemed suitable for extirpative surgery was very much lower than that found by Brock (11 per cent.) in 1948. This low figure is probably accounted for partly by the closure of some thoracic surgical units during the war, but to a much

greater extent by the completely unselected nature of the cases, and is more likely to represent the true rate of operability. From the figures relating to treatment it appears that deep X-ray therapy prolongs life longer, on the average, than extirpative surgery. Patients who had had pneumonectomy died either after a recurrence of the growth in the opposite lung or elsewhere, or from bronchopneumonia in the remaining lung.

Conclusions

Although the period covered by the survey is relatively short, certain features of interest emerge from the data after analysis. In spite of the strong personal impression of the authors to the contrary, it was shown in comparing the triennia 1936–8 and 1945–7 that the incidence of carcinoma of the bronchus did not increase in relation to the other common sites of primary carcinoma. The proportion of bronchial carcinomata to all forms of malignant disease remained nearly constant. The reputed increase in the incidence of these growths during the period under review would thus seem to be more apparent than real. The great preponderance of the disease in men was again confirmed, the proportion of male to female patients being almost six to one. Despite the greater longevity of women, the peak incidence of the disease in women was at a slightly later age than in men, a fact which was found to be of statistical significance. Occupational factors did not appear to be related to the occurrence of the disease, but, as stated above, the information available was very inadequate. The high proportion of men who gave a long antecedent history of cough and chronic bronchitis may be of importance, for these symptoms may have been related to heavy smoking, which has been thought by some to be a factor in the aetiology of carcinoma of the bronchus. Other previous diseases of the chest, including tuberculosis, were shown to be of no significance. As might be expected of a growth so liable to early and widespread dissemination, the symptoms and signs were extremely variable, but the combination of cough, dyspnoea, and pain in the chest was so constant as to suggest that neglect of this triad of symptoms in persons over 40 years old may prevent the discovery of many early cases of bronchial carcinoma. Small and often repeated haemoptysis was observed much more commonly in men than in women, and may have been related to the greater frequency of chronic bronchitis in men. The sites of origin of the tumour showed little difference between the two lungs. The small proportion of peripheral neoplasms conforms to the usual findings of other authors. A plea is made for the abandonment of the term 'Pancoast tumour', as these growths differ in no way from other bronchial carcinomata except that they occur in or near the apex of the upper lobe, and invade the apical region of the pleural cavity and the root of the neck at an early stage. Minute primary growths in the lungs, with widespread and massive secondary deposits in other organs, may render diagnosis of the primary tumour very difficult, but histological examination of an accessible secondary deposit will often leave little doubt as to the primary site. The position of pulmonary neoplasms in relation to the pulmonary circulation often leads to very widespread blood-borne metastases, and no organ

is exempt. The liver was found to be more frequently involved than any other organ, and sometimes the growth was so extensive that the enlargement of the liver, and terminal jaundice due to intrahepatic biliary obstruction, overshadowed all other symptoms and signs caused by the bronchial tumour. The tumours were divided into five histological types, but considerable pleomorphism was found. The oat-celled carcinoma showed less variation in structure, both in the primary and in the metastatic growths, and accounted for 36 per cent. of all bronchial carcinomata. The adenocarcinomata, despite their more differentiated character, were highly malignant. The prognosis in all the varieties of growth was uniformly bad, but survival was longest in the metaplastic squamous-celled group, and these growths gave rise to fewer metastases. It is possible that the latter group accounts for some of the slowly growing tumours which remain symptomless for a period of years. The average age of incidence varied very little between the varieties of growth, and their differences in this respect were not significant.

The failure of ordinary X-ray examination to reveal a growth in the chest was not surprising in view of the secondary pathological changes in the lungs, which masked the underlying causative lesion. A negative radiological report should not engender a feeling of security. Bronchoscopy, and examination of the sputum for malignant cells, were shown to be indispensable where doubt existed as to the possible presence of a growth. The results of treatment were uniformly disappointing, and the small number of cases considered suitable for extirpative surgery served to show the late stage at which the disease was usually met with in a totally unselected series. Of the different methods of treatment employed, deep X-ray therapy offered the best means of prolonging life for a few weeks. Until new methods of treating bronchial and other forms of malignant disease replace the present largely palliative methods, the only way of improving the appalling prognosis for patients suffering from bronchial carcinoma appears to be an earlier diagnosis, with a better chance of complete surgical removal.

We wish to acknowledge the encouragement and help we have received from Dr. A. B. Bratton and Professor W. G. Barnard in the preparation of this paper, and to thank the numerous Medical Superintendents of the former London County Council Hospitals who have co-operated by allowing us free access to the clinical notes of the cases. We are indebted to Mr. B. Benjamin, Statistician to the Public Health Department, London County Council, for his help in the preparation of the Tables, and to Mr. G. W. Moore for the photomicrographs.

Summary

1. The clinical and pathological data obtained from 866 fatal cases of carcinoma of the bronchus have been analysed statistically.

2. No increase was found in the incidence of the disease compared with that of other common forms of carcinoma.

3. The late stage at which the disease was first discovered usually precluded the use of all but palliative forms of treatment. In many cases the first symptoms were caused by secondary metastases.

4. The frequent association of cough, dyspnoea, and pain in the chest as presenting symptoms in carcinoma of the bronchus should prompt careful investigation, including bronchoscopy and examination of the sputum, in the case of any person over 40 years of age who complains of these symptoms.

5. Metastases occur most frequently with adenocarcinomata, and least frequently with squamous-cell growths.

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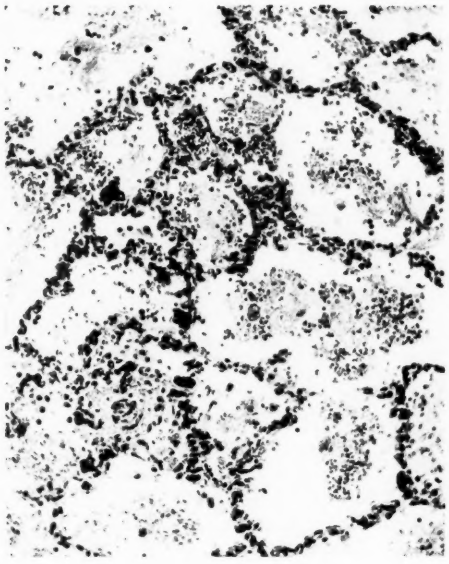

FIG. 3. Diffuse intracapillary spread of an oat-celled carcinoma through the lung (haematoxylin and eosin, × 140)

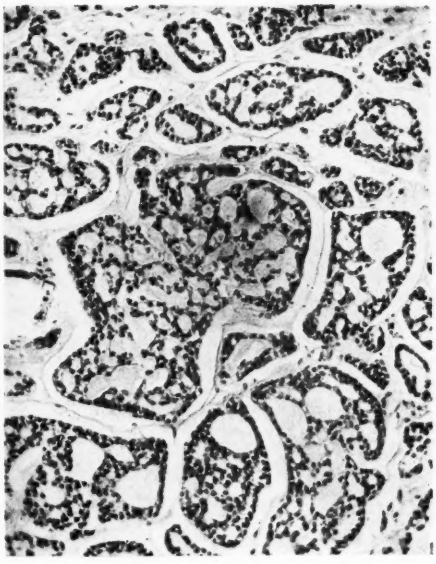

FIG. 4 A primary bronchial carcinoma resembling a benign adenoma in appearance (haematoxylin and eosin, × 105)

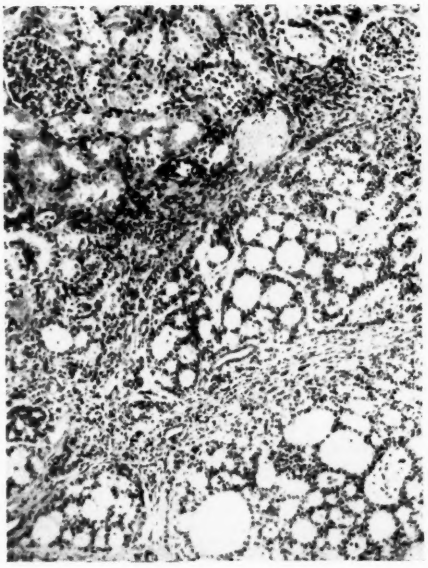

FIG. 5. A metastasis in the kidney from the growth shown in Fig. 4 (haematoxylin and eosin, × 76)

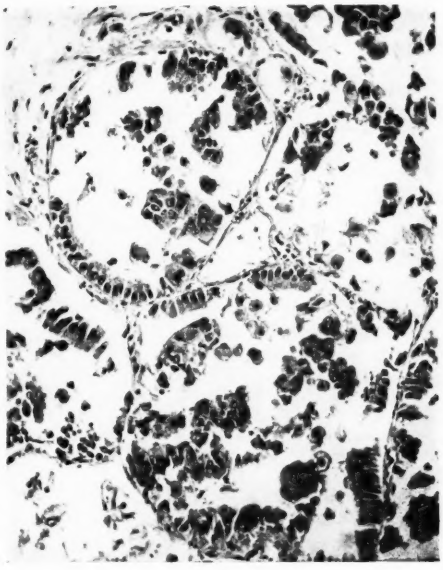

FIG. 6. Lung alveoli lined with malignant mucus-secreting cells in a diffuse pulmonary adenocarcinoma (haematoxylin and eosin, × 140)

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MEGALOBLASTIC ANAEMIA OF PREGNANCY AND THE PUERPERIUM[1]

A Review of Forty-five Cases with Special Reference to their Response to Treatment

By R. B. THOMPSON and C. C. UNGLEY

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This paper is a study of 45 patients, most of whom have been seen by one or both of the authors during the past 17 years. The series includes 22 cases reported by Miller and Studdert (1942), some of which had been referred to in a previous paper (Ungley, 1938). Six cases treated with vitamin B_{12} (Ungley and Thompson, 1950) are also included. Since the type of anaemia in question is frequently stated to be of nutritional origin, dietary factors have been specially investigated. Further evidence has been obtained that the disorder differs fundamentally from Addisonian pernicious anaemia. In three patients increased red-cell destruction has been demonstrated. A follow-up of 26 patients completes the study.

Methods

In 33 instances the diagnosis was established by finding megaloblasts in the marrow or peripheral blood. In the remaining cases a presumptive diagnosis was based on clinical and laboratory findings combined with a typical response to specific therapy with liver or yeast. The haematological methods used are described elsewhere (Ungley, 1949). Before 1947 haemoglobin was estimated by a modified Sahli-Leitz acid-haematin method (100 per cent. = 13·8 gm. per 100 ml.). Thereafter the cyanhaematin method (King and Gilchrist, 1947) was used with a photoelectric colorimeter (100 per cent. = 14·8 gm. per 100 ml.). When the exclusion of extraneous haemopoietic factors was not possible by adequate control periods and dietary restrictions, the results of therapeutic tests were either excluded from consideration or accepted with reserve.

Aetiological Features

Age. The mean age of the patients was 31 years (range 18 to 41 years). In 45 women with Addisonian pernicious anaemia taken at random, the mean

[1] Received January 12, 1951.

age was 55 years (range 34 to 74 years). In Table I 46 cases are arranged according to their occurrence in first or subsequent pregnancies. In Table II these figures are compared with those of births in the rest of the country (*Maternity in Great Britain*, 1948) and with those from a recent survey of 1,000 consecutive births in Newcastle-upon-Tyne (to be published). The distribution of cases suggests that the disorder tends to occur more frequently after multiple pregnancies than in the first or second pregnancy. The χ^2 value compared with the all-England figures confirms this impression, although age, as well as multiparity, might be a factor.

TABLE I

Number of pregnancy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	Total
Number of cases	11	9	12	4	4	1	..	2	2	1	46*

* One patient developed the disorder in two pregnancies, and is counted as two cases in tables of analysis.

TABLE II

Number of pregnancy	*Megaloblastic anaemia*		*% of births*	
	Number of cases	%	*All England* %	*1,000 in Newcastle-upon-Tyne*
1st . . .	11	23·9	40·0	42·2
2nd . . .	9	19·6	28·0	28·5
3rd . . .	12	26·1	16·0	14·9
4th and over . .	14	30·4	16·0	14·4
	46	100·0	100·0	100·0

$\chi^2 = 27{\cdot}7$. Degrees of freedom 3. Probability less than 1 in 1,000.

Onset of symptoms. This was usually late in pregnancy or in the puerperium, but in 11 patients symptoms began before the fifth month (Table III).

TABLE III

Time of onset (months)	1st	2nd	3rd	4th	5th	6th	7th	8th	Puerperium	Uncertain	Total
Number of cases	3	3	3	2	3	5	12	3	8	4	46

TABLE IV

Number of further children	*Number of patients*
1	11
2	2
3	1
6	1
	15

Occurrence of the disorder in previous pregnancies. Of the 35 patients who had had previous pregnancies 28 gave no history of anaemia. Of the remaining seven patients two gave a story of persistent vomiting and weakness in an

earlier pregnancy, but details were not available. Two patients had had iron-deficiency anaemias, and a further two gave a vague history of swelling of the feet and general ill health of doubtful significance. Only one patient (Case 16) developed megaloblastic anaemia in a subsequent pregnancy.[1]

Occurrence of the disorder in later pregnancies. Of 26 patients followed up, 15 had further children (Table IV); only the patient mentioned above developed megaloblastic anaemia a second time.[1]

Clinical Features

Only seven patients were seen during pregnancy, the remaining 39 having already been delivered before admission to a medical clinic. Many were critically ill with dyspnoea and extreme lethargy. Some had infections of the urinary tract, chest, or pelvis. Others showed a febrile reaction which responded to specific anti-anaemic treatment alone, and which was considered to be part of the disorder. Fever was sometimes prominent, and led to errors in diagnosis.

The *tongue* was noted as being sore in 18 patients. Atrophy of the papillae was generalized in nine patients, marginal in seven, absent in 15, and was not recorded in 15. The tongue was clean in 20 cases, furred in six, and its condition was not recorded in 20. Ulceration of the mouth was present in five cases, and in two there was excoriation of the angles of the mouth. *Dysphagia* was associated with soreness of the tongue in three patients, in two of whom a burning sensation was felt behind the sternum on swallowing. These oral and oesophageal symptoms improved or disappeared with relief of the anaemia. The *appetite* was recorded in 41 patients: it was good in 13, and poor or absent in 28. Further comment is made on page 194. Improvement occurred rapidly with remission of the anaemia. *Vomiting* occurred in the last months of pregnancy in 27 patients; in 14 of these it was severe, lasting for four months or more. Fifteen further patients either did not vomit, or suffered only from slight morning sickness early in pregnancy. In four cases there was no record. *Diarrhoea* was present in only two patients. One other patient developed transient steatorrhoea seven months after recovery from megaloblastic anaemia of pregnancy; there was no clinical evidence of this disorder at the time of her earlier illness. The *spleen* was palpable in only five of 38 cases. The *liver* was enlarged in four patients, all of whom had congestive heart failure. Symptoms of *circulatory disturbance* were common. Oedema of the ankles was present in 27 patients, an apical systolic murmur was audible in 26, there was lateral displacement of the left cardiac border in 12, and tenderness of the liver in three. Thirty-five patients were specially examined for evidence of *neurological disorder*; none was found. No patient in the present series, and none reported in the literature, has developed neurological complications after folic acid therapy, but the duration of such treatment has been short and the number of cases small. The *optic fundi* were examined in 37 patients. Haemorrhages were present in 13, of whom 11 had red-cell counts of less than 1,000,000 per c.mm. on admission.

[1] Details of a second patient, who relapsed during the eighth month of pregnancy, were not complete at the time of going to press.

Headache was a common symptom in severely anaemic patients; it disappeared rapidly with relief of the anaemia.

Laboratory Findings

Gastric analysis after histamine was performed in 41 cases: free HCl was present in 32, and absent in nine. Free HCl returned later in one patient who initially had achlorhydria. *Initial red blood-cell counts* are given in Table V. Those of 40 cases of nutritional megaloblastic anaemia of pregnancy from India (Kothari and Bhende, 1949) are given for comparison. Tables VI to X give the initial values for reticulocytes, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and white cells, compared with the values in cases of Addisonian pernicious anaemia with a similar degree of anaemia; values for the 40 cases of nutritional megaloblastic anaemia of pregnancy are also given.

Blood films. The appearances were usually very similar to those of Addisonian pernicious anaemia, but macrocytosis, anisocytosis, and poikilocytosis were often less marked. The white-cell counts were often higher. Multiple lobing of the polymorphonuclear cells was usually present. In three instances megaloblasts were found.

TABLE V

Initial Red Blood-cell Counts

Red blood-cells (millions per c.mm.)	*Number of cases*	
	Megaloblastic anaemia of pregnancy	*Nutritional megaloblastic anaemia of pregnancy (Kothari and Bhende)*
Below 1	21	6
1·0–1·49	12	7
1·5–1·99	6	7
2·0–2·49	4	9
2·5–2·99	2	5
3·0 and over	1	6
	46	40

TABLE VI

Initial Reticulocyte Counts

%	*Number of cases*		
	(1) *Megaloblastic anaemia of pregnancy*	(2) *Nutritional megaloblastic anaemia of pregnancy (Kothari and Bhende)*	(3) *Addisonian pernicious anaemia*
Below 1	14	17	20
1–2	9	8	13
2–3	5	9	4
3–5	6	4	3
Over 5	7	2	1
	41	40	41

Note: the column numbering runs through Tables VII–X.

TABLE VII

Mean Corpuscular Volume

c.μ	(1)	(2)	(3)
60–69	1	5	..
70–79	3	6	..
80–89	6	6	1
90–99	5	9	2
100–109	11	6	11
110–119	3	6	15
120–129	6	2	5
130–139	1	..	4
140 and over	2	..	..
	38	40	38
Mean	104·6	92·6	111·7
Standard deviation	19	15	20
Standard error	3	2	3

TABLE VIII

Mean Corpuscular Haemoglobin

μμg.	(1)	(2)	(3)
Below 25	3	13	..
25–29	23	12	2
30–35	16	12	16
Over 35	4	3	28
	46	40	46
Mean	29·8	27·2	35·3
Standard deviation	4·9	6·5	5·4
Standard error	0·7	1·0	0·7

TABLE IX

Mean Corpuscular Haemoglobin Concentration

%	(1)	(2)	(3)
Below 25	5	6	..
25–29	14	17	10
30 and over	19	17	28
	38	40	38
Mean	28·9	29·2	31·4
Standard deviation	4·4	3·5	2·0
Standard error	0·3	0·6	0·3

TABLE X

Initial White-cell Counts

Thousands per c.mm.	(1)	(2)	(3)
1–2	2	..	8
2–3	6	..	12
3–4	6	3	11
4–5	4	8	4
5–6	1	5	4
6–7	7	8	3
7–8	5	7	1
8–10	5	2	..
10–15	4	7	..
15–20	2	..	..
Over 20	1	..	..
	43	40	43
Mean	6·9	7·0	3·4
Standard deviation	4·8	3·0	1·8
Standard error	0·7	0·5	0·3

Price-Jones curves. These are available for earlier cases only (Ungley, 1938; see Table XI). The mean red-cell diameter may be normal with a wide variability (seven cases), or the curve may be similar to that found in Addisonian pernicious anaemia (one case). All the measurements of red blood-cell diameters were made by the same technician. Larsen (1948) has shown that individuals vary greatly in their power of discrimination between dark and light colours, and that this influences their measurements of mean diameter. This individual variation may amount to as much as 0·5μ. It follows that the actual mean diameters may have been higher or lower than those indicated. Consequently the figures for mean corpuscular average thickness and

$$\frac{\text{mean diameter}}{\text{mean corpuscular average thickness}}$$

may be erroneous. The most significant figure according to Larsen is the standard deviation, which does not normally exceed 0·5μ. In our patients this value was exceeded in every case. Some of the curves suggest the presence of at least two cell-populations (see Ungley, 1938, Figs. 2 and 3).

Bone-marrow examination. Megaloblastic erythropoiesis, indistinguishable from that of Addisonian pernicious anaemia, was present in all of the 30 cases in which sternal puncture was performed. In three additional cases megaloblasts were found in the peripheral blood. There were also changes in the white-cell series, with giant segmented myelocytes, metamyelocytes, and macropolycytes.

Serum-proteins. These were estimated in eight cases; the values are given in Table XII. The figures tend to be at the lower limit of normal, but it is not considered that any conclusions can be drawn from such a small series.

Urinary hormone excretion. This was investigated in one patient only (Case 40), during the seventh month of pregnancy. In 24 hours the excretion of

TABLE XI

Red-cell Data in Eight Cases

Case number	*Red cells (millions per c.mm.)*	*Haemoglobin (gm./100 ml.)*	*Packed cell volume*	*Mean corpuscular volume (c.μ)*	*Mean diameter*	*Standard deviation*	*Coefficient of variation*	*Mean corpuscular average thickness*	$\frac{m.d.}{m.c.a.t.}$
8	1·64	5·0	16·9	103	7·25	0·95	13·09	2·49	2·91
9	0·54	1·7	..	..	6·63	1·01	15·22	..	..
10	1·62	5·4	19·8	122	6·89	1·07	15·36	3·26	2·11
12	0·65	2·2	7·7	118	8·98	1·59	17·7	1·86	4·83
13	0·77	2·2	8·3	108	6·92	0·95	13·8	2·87	2·41
14	1·02	3·5	13·8	135	7·08	0·99	14·0	3·43	2·06
15	1·08	3·5	10·0	93*	7·42*	1·19	16·02	..	..
21	1·48	4·8	18·8	127	7·04	0·80	11·36	3·26	2·16

* Not measured on the same blood sample.

TABLE XII

Serum-proteins (gm./100 ml.)

Case number	*Total*	*Albumin*	*Globulin (by difference)*	*Time of estimation*
1	5·54			5 weeks post partum
3	5·44			2 months ,, ,,
4	5·12			2 weeks ,, ,,
5	5·40	4·56	0·84	3 months ,, ,,
6	6·30	4·80	1·50	Puerperium
9	5·12			5 weeks post partum
28	5·71	4·57	1·14	14 days ,, ,,
36	4·80	4·08	0·72	8th month of pregnancy

TABLE XIII

Van den Bergh reaction		*Number of cases*	
		Megaloblastic anaemia of pregnancy	*Addisonian pernicious anaemia*
(units)	*(mg. %)*		
Below 1·0	0·4 and below	7	1
1·0–1·9	0·4–0·7	14	3
2·0–2·9	0·8–1·1	3	13
3·0–3·9	1·2–1·5	2	4
4·0–4·9	1·6–1·9	1	4
5·0 and over	2·0 and over	2	4
		29	29
		(units)	*(units)*
Mean		2·3	3·1
Standard deviation . .		1·9	1·4
Standard error . .		0·07	0·03

ketosteroids was 5·1 mg. (Dr. F. K. Herbert). Professor Marrian, of the Department of Biochemistry, University of Edinburgh, kindly examined two 24-hour specimens of urine with the following results: pregnanediol, 30·3 and 28·5 mg.; total oestrogen (estimated as oestradiol), 11·8 and 12·5 mg. These values are normal.

Evidence of abnormal pigment metabolism or increased red-cell destruction. Only 10 patients had a definite yellow tint reminiscent of Addisonian pernicious anaemia. In 26 patients there was a waxy pallor only; the colouring of the remaining 10 was not recorded. The results of the van den Bergh test in 29 cases are given in Table XIII, together with those from 29 random cases of Addisonian pernicious anaemia. *Methaemalbumin* was absent from the plasma in the six cases in which a test was made. *Erythrocyte fragility* in saline was normal in eight patients; in a ninth there was a slight increase which was of doubtful significance. *The survival rate of transfused normal erythrocytes* was followed in three cases; in each there was an increased rate of elimination. In Case 19 a rapid fall in red-cell counts followed three transfusions. There was no loss of blood, and the patient was a primipara who had never previously had a transfusion. The increased elimination ceased after oral raw liver therapy was begun. In Case 36 there was also a rapid destruction of transfused cells, which was reduced after treatment with folic acid. In Case 42 the fall of the red-cell count after transfusion was extremely rapid. Vitamin B_{12} therapy had no effect, but there was a reduction in the rate of red-cell elimination after folic acid therapy. Further details of these cases, with charts, will be published shortly in collaboration with Dr. W. Walker.

Dietary Histories

Details of the diets of 27 patients are available for assessment. In three the intake was considered to be excellent; there was no history of vomiting, and the appetite was good. Their intake of meat and green vegetables was adequate, and eggs, milk, and fresh fruit were taken in satisfactory amounts. In four patients the diet was not so satisfactory. Eggs and milk were taken either seldom or not at all (both in this and in the next group milk was rarely drunk as such, but was taken in cooked puddings and tea), and meat was eaten less often. One patient disliked meat, and only took it on one day in the week. Two patients suffered from vomiting, but their appetites were good and the food intake was not affected. It is considered that these four patients had diets no worse than those of many pregnant women who did not develop anaemia. In the remaining 20 women either the diets were very poor (especially in meat and green vegetables), or the intake of food was seriously impaired by loss of appetite and persistent vomiting. Two patients could eat no solid food because of soreness of the mouth; these and five others took only soups, commercial meat extracts, milk, or bread soaked in milk, for periods of between two and four months. Such a poor diet can be considered of possible aetiological significance only if it clearly preceded the onset of anaemia; this was the case in 11 patients of this group.

Responses to Treatment

The responses to treatment are summarized in Table XIV. For the purpose of assessment the reticulocyte responses are compared with the values expected from oral liver therapy in Addisonian pernicious anaemia (Riddle, 1930). The erythrocyte increases are compared with those expected from the parenteral administration of a single dose of 10μg. of vitamin B_{12} in Addisonian pernicious anaemia (Ungley, 1949). These standards are not ideal, but have been chosen for want of any which are more suited to the purpose. Reticulocyte responses and erythrocyte increases are assessed as 'good' when they were at least two-thirds, 'moderate' when they were between one-third and two-thirds, and 'poor' when they were less than one-third of the expected increase. Negligible

TABLE XIV

Response to Treatment

Treatment	*Number of cases*		*Results*				
			Good	*Moderate*	*Poor*	*Negative or negligible*	*Not assessed*
Refined liver extract	10	R.R.	0	0	5 (1*)	3	2
		E.I.	0	0	0	8	2
Crude liver extract	11	R.R.	1*	3*	1*	5	1
		E.I.	2*	0	0	6	3
Vitamin B_{12}	6	R.R.	0	0	1	4	1
		E.I.	0	0	0	5	1
Folic acid	7	R.R.	3	3	1	0	0
		E.I.	2	3	0	0	2
Raw liver	16	R.R.	10 (3*)	5	1*	0	0
		E.I.	4	1	0	3	8
Yeast extract	4	R.R.	2	1	0	1	0
		E.I.	1	2	0	1	0

R.R. = reticulocyte response.
E.I. = erythrocyte increase.
* = possible spontaneous remission (e.g. raised reticulocyte count in control period). Where some of the results shown were possibly spontaneous remissions, their number is given in parenthesis.

responses are those within the limits of error or of day-to-day variation. Some responses (marked with an asterisk in Table XIV) are of doubtful significance because of the possibility of spontaneous remission. This applies to all cases in which the reticulocyte counts were raised prior to treatment, although in some the red-cell counts were falling, and also to those in which there was not an adequate control period. Other responses (listed as 'not assessed' in Table XIV) were excluded altogether from the analysis which follows because they were confused by transfusion or by multiple therapy.

Parenteral liver extract. 1. *Refined.* The reticulocyte responses were negative in three cases and poor in five. Either there was no increase of erythrocytes, or the rise was negligible. 2. *Crude.* Eleven patients were treated by injection of

5 to 10 ml. of campolon. The reticulocyte response was good in one, moderate in three, and poor in one, and in all these five patients spontaneous remission was possible. In five patients the responses were negative or negligible. In the case recorded as 'good' there was a reticulocyte peak on the fifth day. The initial red-cell count was 700,000 per c.mm., and reticulocytes 5·6 per cent.; the red-cell count rose to 2,080,000 per c.mm. in 15 days. Although the patient was evidently in spontaneous remission when treatment was given, there may well have been a superadded response to campolon. This is made more probable by a similar, though less striking, occurrence in three other patients. The erythrocyte increase was negative or negligible in six instances and good in two, in both of whom spontaneous remission may have contributed to the result.

Vitamin B_{12}. The results in six patients treated with vitamin B_{12} have been published by Ungley and Thompson (1950). In five patients the dosage was 80μg., and a sixth was given highly concentrated red pigmented material equivalent to 65 μg. of vitamin B_{12}. One patient had a reticulocyte rise of 3·6 per cent. on the sixth day, but there was no increase of red cells. No other patient showed any evidence of a haemopoietic response. Details of a seventh case are given on page 201.

Folic acid. Seven patients were treated with folic acid: three were given 2·5 mg., and three 20 mg., orally daily; one was given 30 mg. intravenously as a single dose. The reticulocyte responses were good in three patients, moderate in three, and poor in one. The erythrocyte increases were good in two patients: the rise in 10 days was from 1,130,000 to 2,240,000 cells per c.mm., and from 2,500,000 to 3,150,000 cells per c.mm. In three patients the increase was moderate: initial levels of 3,190,000, 1,760,000, and 3,150,000 cells per c.mm. rose in 10 days to 3,550,000, 2,200,000, and 3,560,000 cells per c.mm. respectively. The response was obscured by transfusion in two other cases.

Raw liver pulp. Sixteen patients were treated with oral raw liver pulp in doses of 100 to 200 gm. daily; the lower dosage was the more usual. The reticulocyte responses were good in 10 cases, although in three of these spontaneous remission was probable. Five responses were moderate; in one the response was poor, and was possibly due to spontaneous remission. Erythrocyte increases could be assessed in only eight patients; in most of the excluded cases the true red-cell counts were obscured by transfusion. Responses were good in four instances (900,000 to 2,500,000 cells per c.mm. in 16 days, 1,870,000 to 2,850,000 per c.mm. in 15 days, 1,350,000 to 2,910,000 per c.mm. in 13 days, and 2,400,000 to 3,080,000 per c.mm. in nine days). One response was moderate (1,870,000 to 2,580,000 cells per c.mm. in 15 days), and three were negligible.

Yeast extracts. The reticulocyte rise was good in two patients, moderate in one, and absent in one. Erythrocyte increases were good in one patient, moderate in two, and absent in one. One patient was given daily by mouth 50 gm. of an alcoholic extract of yeast, after a seven-day control period during which her reticulocytes were 0·2 per cent. On the 12th day there was a reticulocyte peak of 21·2 per cent., and the red cells rose from 2,180,000 to 2,570,000 per c.mm. in 15 days. Although the reticulocyte response was greater than

expected, the erythrocyte increase was only moderate. Another patient who had a good reticulocyte response and an erythrocyte increase received 60 gm. of marmite daily, as already reported (Ungley, 1938); the initial reticulocyte count was 6 per cent., and although the red-cell counts were falling, spontaneous remission cannot be excluded.

Transfusion. In 21 patients who received transfusions there was no suggestion that the procedure initiated a response, or had other than a temporary effect.

Spontaneous remission. In 16 patients spontaneous improvement made the assessment of treatment difficult. These remissions all followed delivery. In a few instances they may have been due to an improved diet, but more often the diet was unchanged.

Observations before delivery. Of the seven patients seen before delivery six had full blood examinations (Table XV). None showed evidence of spontaneous remission. The red-cell counts at term ranged from 1,520,000 to 3,650,000 per c.mm. After delivery normal levels were ultimately attained. Before delivery responses to treatment were poor in five patients; only one responded well (Case 36).

Diagnosis

The diagnosis can often be suspected from the history and clinical examination. Mild cases are commonly missed, the anaemia being regarded as physiological or due to iron deficiency, for the mean corpuscular volume and mean corpuscular haemoglobin may be normal or below normal (Tables VII, VIII, IX). In doubtful cases the diagnosis can only be made with certainty by examining the bone-marrow or by demonstrating megaloblasts in the peripheral blood. Addisonian pernicious anaemia arising in pregnancy or the puerperium is rare. It may be suspected if there are any neurological manifestations, or if there is a family history of true pernicious anaemia; in cases occurring in England this diagnosis would also be favoured by a response to vitamin B_{12}, and by a permanent need for maintenance therapy. Any suspicion of Addisonian pernicious anaemia would be dismissed at once by the finding of free HCl in the gastric juice after histamine and alcohol.

Prognosis

Wintrobe (1946) stated that the mortality of this disorder was at one time as great as 50 to 75 per cent. In the present series there were no deaths, despite the number of very anaemic patients. Most patients stopped treatment soon after leaving hospital. Among 26 cases followed up for periods of from one to fourteen years there has been only one relapse;[1] this occurred in a second pregnancy. Table XVI shows the duration of the follow-up periods.

Babies. In 46 pregnancies there were 47 live births. Twin pregnancies occurred four times; the expected incidence of twins is one in 80 births. There were three stillbirths, and two infants died shortly after birth. Three died later,

[1] See the footnote to page 189.

TABLE XV

Cases Seen During Pregnancy

Case number	*Month of pregnancy*	*Later observations*	*Haemoglobin* (%)	*Haemoglobin* (*gm./100 ml.*)	*Red blood-cells* (*millions/c.mm.*)	*Reticulocytes* (%)	*Cell-volume* (%)	*Mean corpuscular volume* (*c.μ*)	*Mean corpuscular haemoglobin* (*μμg.*)	*Mea corpuscular haemoglobin concentration* (%)	*Treatment*	*Response*
16	8		67	9·9	3·56	0·2	32	90·0	28·0	31·0	Folic acid	R.R. good
		At delivery	71	10·6	3·68		34	92·4	28·4	31·0		E.I. moderate
		6 weeks later	85	12·4	4·94		44	89·1	25·4	28·6		
30	8		38	5·2	1·76	0·2	15·7	89·0	29·8	35·8	Raw liver pulp	R.R. maximal
		At delivery	47	6·9	2·15	1·6			32·1			E.I. negligible
		18 mths. later	91	13·5	4·61				29·2			
33	7		18	2·5	0·92				27·1		Raw liver pulp	R.R. moderate
		After transfusion	26	3·9	1·35	0·2	12	90	28·9			E.I. negligible
		At delivery	30	4·4	1·52	0·2			28·9			
		2 mths. later	87	12·9	4·48				28·9			
36	8		30	4·4	1·62	1·8	12·1	80	27·1	34·2	Folic acid Transfusion	R.R. good
		At delivery	65	9·6	3·37	2·8	28	83·1	28·6	34·4		E.I. good
		2 mths. later	82	12·1	4·57		38·6	82·3	26·6	31·5		
40	7		43	6·4	1·76	1·0	21·0	120·0	36·1	30·3	Folic acid Transfusion	R.R. moderate
		At delivery	67	9·9	3·65	0·6	33·5	91·8	27·3	29·3		E.I. moderate
		12 days later	82	12·1	4·42					27·4		
43	8		46	6·8	2·90	2·2	26·0	89·6	23·6	26·2	Folic acid	R.R. good
		At delivery	63	9·3	3·50	1·2	32	91·4	26·6	29·1		E.I. moderate
		1 mth. later	89	13·2	5·38		44·0	81·8	24·0	30·0		

R.R. = reticulocyte response.
E.I. = erythrocyte increase.

one at three days (cause unknown), one at three weeks of cystic cerebral degeneration, and one of pyloric stenosis.

TABLE XVI

Duration of follow-up (years)	*Number of cases*
1–3	6
4–7	10
8–11	8
12–14	2
	26

Discussion

The nature of the deficiency. Therapeutic trials with the pure haemopoietic substances now available have not only further emphasized the differences between Addisonian pernicious anaemia and megaloblastic anaemia of pregnancy, but also indicate that the latter is not a homogeneous group. Neither the finding of megaloblastic erythropiesis nor the association with pregnancy and the puerperium implies identity of causative factors. Five cases of megaloblastic anaemia of pregnancy have recently been reported from India by Patel and Kocher (1950). We have compared the responses obtained with those to be expected in Addisonian pernicious anaemia, using the formula of Ungley (1949). The results are given in Table XVII. These responses to vitamin B_{12} are in

TABLE XVII

Responses to Vitamin B_{12} (Patel and Kocher)

Case number	1	2	3	4	5
Dose	5μg.	20μg.	80μg.	20μg.	5μg.
Actual as % of expected response	44	87	112	84	62

contrast to our own, and strongly suggest that the limiting factors in the two groups of cases, tropical and temperate, are different. In the following discussion we shall refer only to cases observed by us in England. In the present series there was seldom, if ever, a response to parenteral liver extract or to vitamin B_{12} in doses more than sufficient to produce a response in Addisonian pernicious anaemia. Similar observations have been made by others (Callender, 1944; Watson and Castle, 1946; Davidson, Girdwood, and Clark, 1948; Bethell, Meyers, and Neligh, 1948; Day, Hall, and Pease, 1949). Megaloblastic anaemia of pregnancy has usually been regarded as due to a deficiency of the anti-pernicious-anaemia principle, brought about either by lack of extrinsic factor from the diet or by a temporary absence of intrinsic factor from the stomach. If this were true the disorder should respond to injection of the liver principle; the observations presented above clearly indicate that some other explanation must be sought. Eight of our patients (including the additional case later described in full) were treated with folic acid; a response resulted in each case. Similar results have been obtained by others (Moore, Bierbaum, Welch, and

Wright, 1945; Spies, 1946; Davidson, Girdwood, and Clark, 1948). This suggests, but does not prove, that there is a state of folic acid deficiency, though how this is brought about is unknown. Some of our patients had extremely poor diets, and in them the anaemia may have been due to a deficient intake of folic acid. Others, however, had normal dietary histories. Many diets, though poor, were no worse than those of patients of similar social status who did not develop megaloblastic anaemia.

Responses to liver pulp and yeast extracts. The responses to liver pulp may have been due to folic acid. Beef liver is said to contain about 10μg. of folic acid per gm. (Moore, Bierbaum, Welch, and Wright, 1945), so that our patients might have been given 1 to 2 mg. daily. As parenteral liver extract had already failed in a significant number of these patients, the observed responses are not likely to have been due to oral vitamin B_{12}. The nature of the active substance in yeast extracts is unknown. In one patient the urinary excretion of folic acid was negligible during treatment with alcoholic extract of yeast, but a normal proportion was excreted later during folic acid administration. This and other evidence (Watson and Castle, 1946) suggests the existence of another haemopoietic (? Wills's) factor.

Evidence of increased red-cell destruction. Haemolysis in cases of megaloblastic anaemia of pregnancy has been noted previously, but clear evidence of its degree has been lacking. Lescher (1942) reported, with nine examples of 'temporary pernicious anaemia of pregnancy', eight cases of 'haemolytic anaemia of pregnancy'. In five of the latter the marrow was megaloblastic, and it appears likely that these cases were examples of megaloblastic anaemia of pregnancy with increased red-cell destruction. Callender (1944) noted that some of her patients showed a fall in red cells of as much as 3 per cent. per day, which could only be accounted for by an increased destruction of cells. In one of her patients the survival of transfused red cells was followed with the Ashby (1919) technique. The average life of the transfused cells was 25·9 days, compared with 50 days in a control group of patients with hypochromic anaemia. The nature of the agent responsible for this increased rate of elimination in certain patients is obscure. Further evidence of the role of haemolysis in megaloblastic anaemias has been obtained, and will be published shortly.

Hormonal theory. Day, Hall, and Pease (1949) have reported an abnormal pattern of urinary hormone excretion in megaloblastic anaemia of pregnancy. Only one case of the present series was investigated, but no abnormality was found. The question is worth investigating whether an abnormal steroid antagonistic to folic acid is produced by patients with pernicious anaemia of pregnancy. It may be of significance that a sex hormone, dehydroisoandrosterone acetate, has folic-acid-like effects on certain micro-organisms (Gaines and Totter, 1950).

Conclusions

Aetiological. None of the theories so far put forward satisfactorily explains the aetiology of all cases of this disorder. The only common factor is the close

relationship to pregnancy. Dietary deficiency was of possible significance in only 11 out of 27 of our patients.

Therapeutic. Severely anaemic patients may require an initial small transfusion given slowly by drip. Parenteral extracts of liver and vitamin B_{12} are without effect, at least in many of the cases occurring in temperate climates. Folic acid, in doses of 10 to 20 mg. daily by mouth, is recommended as the most satisfactory treatment. Iron therapy may be required during recovery, when hypochromia often becomes manifest. Treatment should be continued for one to two months after the blood counts reach normal levels. In any subsequent pregnancy the patient should return for periodic blood examinations. She should be told of the rarity of relapses, and should never be advised against increasing her family.

Additional Case

The following recent case is not included in the Tables of analysis. It is reported in full because it exemplifies the difficulties of diagnosis, and because the patient's responses to treatment are of interest.

Mrs. M. E. H., aged 36 years, was referred to hospital in the sixth month of her fourth pregnancy because of anaemia. There had been no vomiting, her appetite had been good, and she had taken a diet adequate in meat, vegetables, fruit, and milk. The only abnormal clinical findings were anaemia and generalized partial papillary atrophy of the tongue. No neurological abnormality was found. In previous pregnancies she had been well. The initial blood findings were: red cells 3,480,000 per c.mm., haemoglobin 48 per cent. (7·1 gm. per 100 ml.), colour index 0·69, white cells 8,000 per c.mm., cell-volume 27 per cent., mean corpuscular volume 77·6 c.μ, mean corpuscular haemoglobin 20·4 $\mu\mu$g., and mean corpuscular haemoglobin concentration 27·0 per cent. Hypochromic anaemia was diagnosed, and she was treated with an intravenous iron preparation. After 14 days the counts remained virtually the same, and she was admitted to hospital, where the following observations were made. Erythropoiesis was megaloblastic. Free HCl was present in the gastric juice after histamine and alcohol. The plasma-bilirubin was 0·64 mg. per 100 ml.; the direct reaction was negative. Methaemalbumin was absent. A fat analysis for six days on a diet containing 50 gm. of fat daily showed that 88 per cent. of the fat was absorbed. The Wassermann and Kahn reactions were negative. Liver function tests were as follows: zinc sulphate turbidity 6 units, thymol turbidity 1 unit, thymol flocculation 0, cephalin-cholesterol +. After a five-day control period the counts were: red cells 3,220,000 per c.mm., haemoglobin 45 per cent. (6·7 gm. per 100 ml.), reticulocytes 0·6 per cent., colour index 0·70, white cells 3,300 per c.mm., cell-volume 24·5 per cent., mean corpuscular volume 76·1 c.μ, mean corpuscular haemoglobin 20·7 $\mu\mu$g., mean corpuscular haemoglobin concentration 26·9 per cent. On this day 160μg. of vitamin B_{12} were administered parenterally; there was no response (see Figure). Alcoholic extract of yeast was then given orally in daily doses of 20 ml. (equivalent to 200 gm. of dried yeast) for 15 days. There was a reticulocyte peak of 12·4 per cent. on the 10th day, but no increase of red blood-cells. On the 15th day the counts showed red cells 2,230,000 per c.mm. and haemoglobin 35 per cent. (5·2 gm. per 100 ml.). Folic acid, 2·5 mg. a day intramuscularly, was next given for 10 days. There was a reticulocyte peak of 21·2 per cent. on the fifth day, and by the 10th day the counts showed red cells 3,160,000 per c.mm. and haemoglobin 55 per

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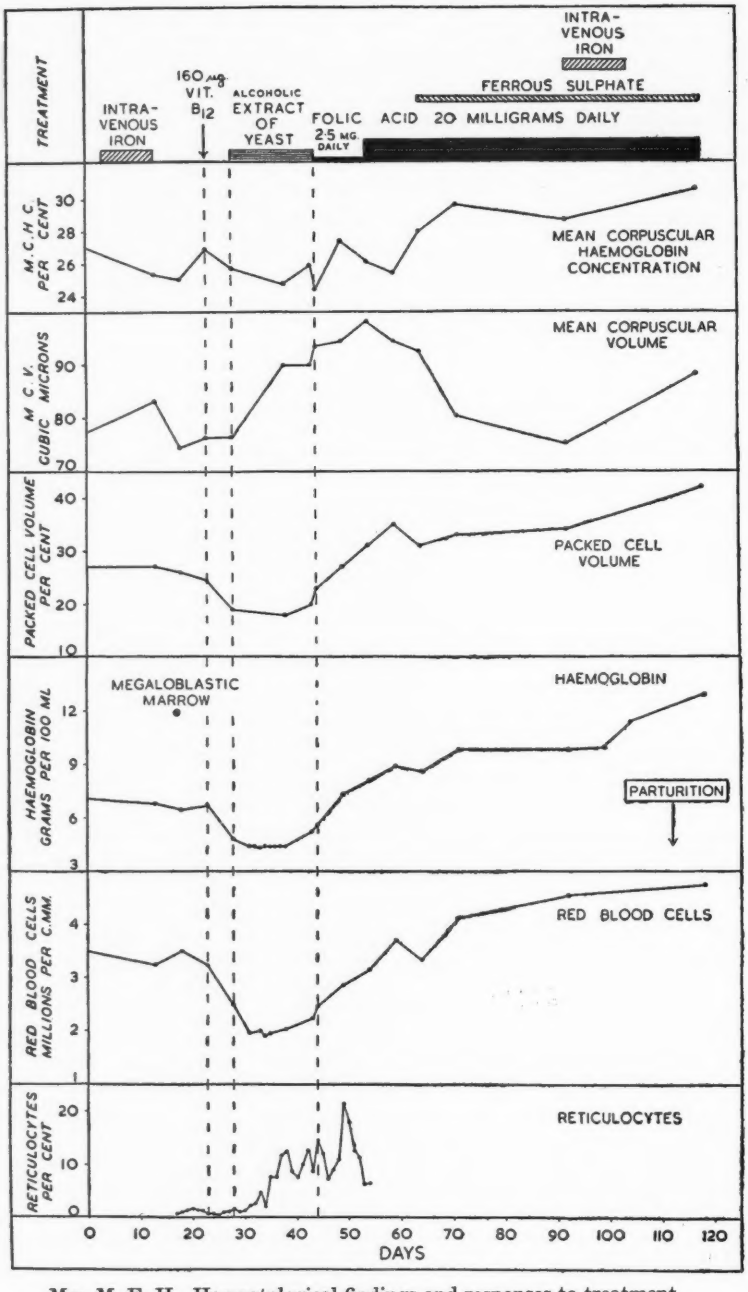

Mrs. M. E. H. Haematological findings and responses to treatment.

cent. (8·1 gm. per 100 ml.). She was then given 20 mg. of folic acid daily by mouth, later supplemented by iron, and was seen at intervals during the rest of her pregnancy. The highest count reached before delivery showed red cells 4,530,000 per c.mm., haemoglobin 66 per cent. (9·8 gm. per 100 ml.), colour index 0·73, white cells 8,300 per c.mm., and mean corpuscular haemoglobin 21·5$\mu\mu$g. When she was seen six days after delivery her blood count showed red cells 4,750,000 per c.mm., haemoglobin 87 per cent. (12·9 gm. per 100 ml.), colour index 0·92, white cells 4,000 per c.mm., cell-volume 42 per cent., mean corpuscular volume 88·4 c.μ, mean corpuscular haemoglobin 27·2$\mu\mu$g., and mean corpuscular haemoglobin concentration 30·6 per cent.

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Summary

1. Forty-five cases of megaloblastic anaemia of pregnancy and the puerperium are described, together with their responses to various forms of treatment—yeast extracts, raw liver pulp, parenteral liver extracts, vitamin B_{12}, and folic acid.

2. With a few doubtful exceptions no patient has been found to respond to the anti-pernicious-anaemia principle, either in its pure form as vitamin B_{12} or as parenteral liver extract.

3. Patients have been shown to respond to folic acid, raw liver pulp, and yeast extract. The responses to yeast cannot be satisfactorily explained; those to liver pulp may have been due to folic acid.

4. The frequent lack of response to the anti-pernicious-anaemia principle seems to rule out the earlier view that all such cases arise from a deficiency of Castle's intrinsic or extrinsic factors.

5. The dietary histories have been investigated in 27 cases; in only 11 of these could the anaemia be explained on a deficiency basis.

6. Evidence of increased red-cell destruction is given in three cases.

7. Suggestions are made regarding treatment.

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AMINOACID METABOLISM IN CYSTINURIA[1]

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With Plate 21

Cystinuria has been known as a metabolic curiosity since 1810, when Wollaston first described a stone of unusual composition which he had obtained from a human bladder. It was soon discovered that the component substance, to which the name cystine was given, was constantly present in grossly excessive quantities in the urine of patients who had this kind of stone, and that it could be detected microscopically as characteristic flat hexagonal crystals in the urinary deposit. In patients with this abnormality there was a tendency to kidney damage, which was often severe enough to be the cause of death. The mechanism of the disorder was studied by Garrod (1923), and was ascribed by him to an 'inborn error of metabolism'. By this he implied that there was a hereditary defect, present from birth or earlier, due to the absence of a single enzyme which was essential for the first stage in the further metabolism of cystine in the body. As a result of this defect a 'metabolic block' occurred, and the cystine, which would normally be broken down to more simple constituents, accumulated in the body and was in consequence excreted, largely unchanged, into the urine. Garrod likened the metabolic defect to that occurring in other congenital disorders, for instance in alkaptonuria, pentosuria, and porphyrinuria, in which he again assumed that enzymes were missing which were essential for the further metabolism of homogentisic acid, pentose, and porphyrins respectively. Garrod's views have continued to hold the field, although many have shown that the chemical simplicity that should follow from the occurrence of such a metabolic block does not in fact obtain in cystinuria. (For a further elaboration of this point see Dent, 1950.) For instance, it has been claimed that in many cases of cystinuria putrescine and cadaverine may be isolated from the urine in grossly abnormal quantities (see the review of literature in Garrod, 1923). Moreover, cases of cystinuria have been described in which other aminoacids such as lysine (Ackerman and Kutscher, 1912), tyrosine and leucine (Abderhalden, 1919) are excreted with the cystine in excessive quantities. As a consequence most modern authors (for example Peters and Van Slyke, 1946) have tended to be cautious in their interpretation of the mechanism of cystinuria. The difficulties encountered in the past can be illustrated by the contrast between the following statements: 'The excretion of cystine is not simply an index of a general

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disturbance in the metabolism of the aminoacids, but a definite entity confined to cystine' (Looney, Berglund, and Graves, 1923), and 'The data presented are in accord with the view that in cystinuric patients the metabolism of aminoacids may be deranged in several respects, and not only with regard to cystine' (Yeh, Frankl, Dunn, Parker, Hughes, and György, 1947). Considerable confusion also exists on the clinical side. The damage often found in the kidney has been ascribed not only to the result of stone formation but also to direct damage to the kidney by the excessive quantities of cystine excreted (Russell and Barrie, 1936; Fanconi, 1946). Yet cystinuria has often been found in otherwise healthy adults. On the other hand there is a condition, usually called 'cystinosis', which is invariably fatal at any early age, and in which the outstanding biochemical feature is that widespread deposits of cystine crystals are found in the body tissues. This disease may or may not be associated with an increased cystine excretion. The position was greatly clarified by Lewis (1932), who tested 10,534 samples of urine from healthy students with more simple and reliable chemical tests for cystine than had been used before. He found 18 undoubted cases of gross cystinuria, with 22 further cases showing lesser degrees of the condition. This result demonstrated that the excretion of cystine was much commoner than was previously thought, was only rarely associated with demonstrable disease, and occurred in varying degrees of severity, some not easily distinguishable from the normal. In spite of this the suggestion has persisted, even in a recent review (Freudenberg, 1949), that the many clinically distinct syndromes associated with cystinuria and cystinosis are different manifestations of the same inborn metabolic error.

In some preliminary aminoacid analyses of the urine of adult patients in whom cystine stones had been found we noted that the urine invariably contained large quantities of lysine, and nearly always of arginine, in addition to cystine; the other aminoacids were present in about the usual concentrations. In any given case which was followed for a few years the aminoacid pattern in the urine was fairly constant. This constancy recalled the findings in another hereditary condition, the Fanconi syndrome (Dent, 1947, 1948*a*), in which much larger numbers of aminoacids, as well as glucose, are excreted in the urine, and in which the pattern, although varying from case to case, is very constant in any one patient. In the Fanconi syndrome a low renal threshold for aminoacids and glucose seemed to be the immediate cause of the aminoaciduria and renal glycosuria. This suggested the possibility of a similar explanation in the case of cystinuria, an explanation which would also better account for the abnormal quantities of substances in the urine, such as lysine and arginine, which appear to have no metabolic relationship to cystine. A low renal threshold for cystine had already been suggested as a possible explanation of the cystinuria (Brand, Harris, and Biloon, 1930; Cleland, 1946; Duncan, 1947; Addis, 1948), but so far as we are aware no proof had been attempted, and all previous systematic studies had been based on the more commonly held theory of an error of metabolism affecting all body tissues, or possibly only the liver, rather than one affecting the kidney tubules. We decided, therefore, to study more samples of

urine from cases of cystinuria, and to carry out aminoacid analyses of the plasma from as many cases as possible. We have confined the present study to the most common and typical form of classical cystinuria. The urine of all our 15 patients gave a strongly positive cyanide-nitroprusside test for cystine (Brand, Harris, and Biloon, 1930). In addition they had had no serious disease, except such as might be the result of minor renal damage. Eight of them had had stones or renal colic, five were close relatives of one or more of these eight patients, and the remaining two were asymptomatic cases discovered by routine urine-testing. A preliminary account of the work reported here has already appeared (Dent and Rose, 1949). A genetic study, which includes other conditions in which an excessive excretion of cystine occurs, is being reported elsewhere (Dent and Harris, 1951).

Methods

Urine and plasma samples were examined by paper chromatography, and plasma from two patients and one control by microbiological assay. Brief clinical summaries are to be found in Appendix A at the end of the paper.

Collection of urine. Fresh specimens of urine were normally stored at 4° C with a crystal of thymol. In a few cases they were sent by post. They were rejected if obviously contaminated with bacteria. When a plasma sample was taken a specimen of urine was always collected within a few minutes, so as to provide approximately simultaneous samples of the two fluids.

Preparation of plasma for analysis. Twenty- to thirty-millilitre samples of venous blood were withdrawn with dry needles and syringes, and placed in vessels containing heparin. They were centrifuged as soon as possible and the plasma, which was never contaminated by haemolysis, separated. The plasma-proteins were removed by ultrafiltration through collodion membranes, as described by Dent and Schilling (1949). The ultrafiltrate was used for the microbiological assays. Before chromatographic analysis it was desalted in a micro-modification (Dent, 1951) of the electrolytic apparatus of Consden, Gordon, and Martin (1947).

Acid hydrolysis of urine. This was carried out with 6N HCl at 100° C for 24 hours. The final solution was evaporated *in vacuo* to remove the excess of HCl.

Paper-chromatographic analysis for aminoacids. This was done only by the two-way (two-dimensional) technique of Consden, Gordon, and Martin (1944), since one-way methods are insufficiently specific for the analysis of aminoacids in biological fluids. As first solvent phenol was used in the presence of NH_3 and HCN vapours. A collidine-lutidine mixture (Dent, 1948*b*) was used as second solvent. All chromatograms were performed first on the untreated urine, then again after oxidation with H_2O_2 and ammonium molybdate to show up cystine and methionine, if present (Dent, 1947), and in a few cases also after acid hydrolysis to destroy peptides.

Microbiological assay for cystine. This was carried out by Dr. W. Cuthbertson of Glaxo Laboratories on two cystinuric plasmas and one normal. He used the

method of Dunn, Shankman, Camien, Frankl, and Rockland (1944) using *Leuconostoc mesenteroides* P 60, but the final volume employed was 2 ml. instead of 10 ml. as in the published method.

Results

Plasma and urine analyses. Plasmas were analysed from seven of our 15 cases of cystinuria. Six cases (L., A. L., S. L., I. W., St., and H.) gave chromatograms identical in all respects with those we have repeatedly obtained from normal people. Since the chromatograms showed spots for all the 20 common aminoacids except tryptophane and hydroxyproline, as well as for a few rare aminoacids, it appeared that there could not be any gross disorder in the concentrations of any of these substances in the plasma. The seventh case (P. W.) was normal except for the presence of traces of the unknown basic aminoacid 'fast-arginine' (Dent, 1948*b*), and this substance was not constantly present. It moves on the chromatogram to a position very close to that occupied by putrescine and cadaverine. An attempt to prove that it was not either of these compounds, and to investigate its composition in a preliminary fashion, is described in Appendix B. It must be emphasized that our method of comparing quantities of aminoacids on the chromatograms, by visual comparison of the strengths of colour with ninhydrin, is only accurate to about ± 30 per cent. Since, however, the urinary output of cystine in a cystinuric subject is 10 to 20 times as great as normal, a raised plasma-cystine level, if sufficient to account for the urinary output, would be readily detectable in our chromatograms. Specimens of urine were examined from all the patients, and almost invariably gave chromatograms closely resembling that reproduced in Plate 21, Fig. 2 (*b*); that is, the outstanding feature was the greatly increased concentration of cystine, lysine, and arginine, the other aminoacids present varying within the normal range. Repeated samples were taken in most cases, over a maximum period of four and a half years. Some minor exceptions noted in this constancy of the urinary pattern were as follows: *Cases A. L. and S. L.* The original specimens of urine from both these identical twins were sent by post, and showed the presence of no arginine, but of a definite excess of citrulline, confirmed by the use of markers on the chromatograms. Citrulline has never been found in subsequent fresh specimens, nor in the urine of any other cystinuric subjects, and it had disappeared from the original specimens after a year's storage at 4° C. The patterns in all the more recent specimens of urine from these two patients have been quite typical. We suggest that the original finding may have been due to bacterial action on the arginine which was almost certainly present in the original urine. An early report which we made of the finding of citrulline has been quoted by Albright and Reifenstein (1948); we now think that we should withdraw that statement. *Case P. W.* The quantity of 'fast-arginine' found in the urine has been variable. Sometimes it has been almost undetectable, at other times it has given a very definite and strong spot on the chromatograms. It has been absent in all her recent specimens, very many of which have been analysed. *Cases Sch. and H.* Occasional specimens analysed (containing 250 μg.

of total nitrogen) have failed to show the presence of arginine. Arginine could be detected when more urine was analysed on the chromatogram, and its concentration was greater than normal, though less than usual in cystinuria.

Acid hydrolysis of urine. This was carried out in specimens of urine from L. and P. W. The chromatograms showed the usual changes found on hydrolysing normal urines, namely, a large increase in aspartic and glutamic acids with very slight, but probably significant, increases in various other aminoacids such as valine, leucine, and proline. The cystine content did not appear to increase, as would be expected if it had been excreted in the form of an easily broken-down complex.

Microbiological assays. The cystine levels were found to be as follows (μg./ml.): normal plasma, 10; cystinuric plasmas: Case P. W., 15; Case S. L., 8.

Chromatographic estimate of the 24-hour output of cystine. We have not yet attempted a quantitative assay. In our opinion no accurate quantitative method based on paper chromatography is yet available. But a rough idea of the order of quantity may be obtained. A two-second urine specimen from Case H. gave a cystine spot of a colour-strength roughly equivalent to that given by about 20 μg. of cystine. This rate of excretion is of the order of 1 gm. a day. By using a similar method we have estimated that all the patients excrete about the same quantity. The normal 24-hour output of cystine is 30 to 100 mg. per day, and usually in the lower levels of this range.

Discussion

Our results indicate that the 15 cases of cystinuria studied resembled each other closely in showing a constant excretion in the urine of large quantities of cystine and lysine, and nearly always of arginine. The group selected according to our stated criteria appeared to be quite homogeneous and, since several patients were close blood relatives (Appendix A), the condition was also capable of breeding true to type. There was no suggestion of overlap with any of the other clinical syndromes (Fanconi syndrome, cystinosis, Wilson's disease) in which an excessive cystine excretion may occur. Moreover, such evidence as we have (Dent and Harris, 1951) suggests that these other syndromes are genetically, as well as biochemically and clinically, distinct from that shown in our 15 cases. In these syndromes a gross aminoaciduria occurs in which large quantities of very many (10 to 20) aminoacids are excreted, and the cystine excretion in itself appears to play a relatively small part. It therefore appears that we cannot readily interpret some of the earlier reported cases of 'cystinuria', such as those of Abderhalden (1919), in which the diagnosis was made as the result of a test for cystine only. In the present state of our knowledge the only condition in which a pure 'cystinuria', that is an excretion of cystine in gross disproportion to all the other aminoacids, is known to occur is chronic liver disease (Dent and Walshe, 1950). For these various reasons we cannot accept the view (Freudenberg, 1949) that the cystinurias, and also cystinosis, are all variants of the same inborn error of cystine metabolism. In contrast to the urinary findings, the plasma in the seven cases studied was comparatively

normal. The plasma-cystine level was certainly not raised when determined chromatographically or (in two cases) microbiologically. We conclude that the gross cystinuria must be due to a 'low renal threshold', not to a failure to metabolize cystine in the body.

Our present concept of this type of cystinuria is therefore as follows. The aminoacid metabolism is normal so far as the liver and body tissues are concerned; each tissue is supplied with, and can metabolize in the usual manner, all the aminoacids necessary to normal working. The cystinuric individual therefore grows well, is normally resistant to disease, and is clinically indistinguishable from normal; but as a result of an inherited defect of the renal tubules he is only able to reabsorb from the glomerular ultrafiltrate about one-half of the cystine present, and a small but unknown proportion of the lysine and arginine. These substances are therefore concentrated in the urine to a degree which may reach twentyfold of normal. This concentration in itself causes no damage to the kidney, since the glomerulus filters no more cystine than in a normal person, and the tubules obviously handle much less than usual. The cystine is very insoluble, and the urine passed is therefore supersaturated when excreted, and tends on standing to deposit the characteristic crystals, especially when the urine is acid and the cystine is therefore nearer to its isoelectric point. In a small proportion of cases other factors operate to cause crystallization of cystine in the renal tract, resulting in a cystine aggregate which, once formed, will tend to grow into a macroscopic stone. This stone may cause colic if passed, or may predispose the patient to the usual sequelae of any kind of stone: chronic infection from urinary stasis, hydronephrosis, pyelonephritis, hypertension, or uraemia. The amount of cystine passed into the urine in a cystinuric subject at any given moment will depend on the blood cystine level and on the glomerular filtration rate. One might therefore expect, as other workers have already shown, that the 24-hour output of cystine will vary very much from day to day, even if the intake of sulphur-containing aminoacids is kept constant. Moreover, as the body avails itself of, and can metabolize, all the cystine that it requires, the amount appearing in the urine will only represent a variable and minor proportion of the combined intake of cystine and of cystine-forming substances such as methionine present in the diet, and no cystine deficiency is likely to occur. Nor is there any reason why an excess of cystine should be present in the body fluids or tissues. The increased cystine output reported to occur after feeding cysteine and methionine, but not cystine, to cystinuric subjects (Brand, Cahill, and Harris, 1935) is explicable on the basis of the resultant changes in the blood cystine level. We suggest that cysteine feeding produces a large increase in cystine output because the cysteine is very soluble, and is therefore rapidly absorbed, causing a large rise in the blood cystine or cysteine levels. Cystine is very insoluble, and is therefore likely to be slowly absorbed after feeding. It can therefore be more efficiently removed from the portal blood by the liver, and will only result in small rises in the cystine level of the systemic blood. This will not show itself as an increased cystine output when merged into the

relatively large spontaneous variations of 24-hour excretion. Since the known facts can be explained in this manner, there is no reason to put forward the improbable theory that there are different metabolic paths in the body for cystine and cysteine (Brand, Cahill, and Harris, 1935). Methionine is soluble, and is therefore rapidly absorbed from the gut. It is known to provide sulphur for cystine formation, and presumably causes an appreciable rise in the blood cystine level, and thus an increased output of cystine. We are now attempting

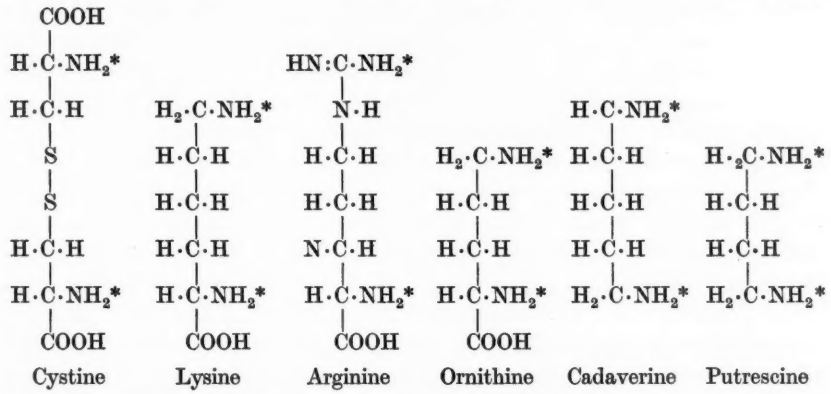

FIG. 1. Structural chemical formulae. Cystine and lysine are always excreted together in excessive quantities in cystinuric urines, and arginine nearly always. Note that these three compounds resemble each other in possessing basic groups (marked *) separated by about equally long chains of atoms. Ornithine, cadaverine, and putrescine may or may not occur occasionally in cystinuric urine; none have been definitely found in any of our cases. They show gross structural resemblances to the first three compounds, but the chain between the basic groups tends to be shorter.

to check by more direct means these views of sulphur-aminoacid metabolism in cystinuric subjects (Dent and Joron, 1951). The small increases of cystine excretion which have been stated to occur after feeding alanine and other non-sulphur-containing aminoacids (Cleland, 1947) might be due to an ensuing increase in the glomerular filtration rate. Such an increase occurs in the dog after feeding glycine (Pitts, 1944) or after a high protein diet (Jolliffe and Smith, 1931–2; Pitts, 1944).

The occurrence together in the urine of aminoacids of such different molecular structure as cystine, lysine, and arginine is not likely to be due to an error of metabolism. But their gross structural resemblances suggest that the cause might be the failure of a common mechanism of tubular reabsorption. In the case of lysine and arginine, evidence of such a common mechanism has already been provided by Wright (1948). All three aminoacids contain two basic groups separated by a chain of four to six atoms (Fig. 1). It is conceivable that the same tubular mechanism of reabsorption (defective in cystinuric subjects) deals, perhaps by N-phosphorylation, with molecules of this general shape, and cannot distinguish between them. Though this is pure speculation, it is at any rate impossible with our present knowledge to propose a metabolic (rather than, as above, a physiological) explanation for the constant excretion together of these

substances. Such a confusion between molecules is already very familiar in the form of the substrate competitions which occur in the field of bacterial metabolism, for instance in the competition between sulphanilamide and *p*-aminobenzoic acid. It is to be noted that in the other renal aminoacidurias, such as the Fanconi syndrome, a similar excessive excretion of lysine, and usually of arginine, is again the invariable accompaniment of a gross cystinuria (Dent and Rose, unpublished work), while in the 'hepatic cystinurias' of Dent and Walshe (1950) the excretion of cystine, almost certainly the result of a raised blood cystine level, occurs usually without lysine and arginine. The fact noted by Lewis (1932) that the extent of cystine excretion is variable in different cystinuric subjects, and that therefore it is impossible to draw a clear line between normal and abnormal, also makes it difficult to accept cystinuria as an 'error of metabolism' in the sense used by Garrod. In the case of alkaptonuria and phenylketonuria there is never room for doubt, on chemical grounds at least, in the diagnosis. Each may be described as an 'all or none' condition—the patient either has it or does not have it—and the abnormality in question, an increased excretion of homogentisic acid or of phenylalanine and phenylpyruvic acid, is very definite. Both conditions could therefore be ascribed to the complete absence of certain enzymes and the consequent production of a metabolic block. In the case of phenylketonuria, for instance, it appears that the enzyme which is necessary to effect the first stage in the metabolism of phenylalanine is under direct genetic control, as in the case of the enzymes studied with the aid of mutants of *Neurospora crassa* (Beadle, 1945). The enzyme is completely absent in affected individuals, who therefore show a complete 'inborn error of metabolism'. Although the whole clinical picture varies slightly from case to case, the demonstrable chemical abnormality—a very high plasma level of phenylalanine—is consistently 'all or none', being the immediate metabolic result of an 'all or none' genetic abnormality. In contrast to this condition the demonstrable chemical abnormality in cystinuria—an increased output of cystine in the urine—is variable, being the consequence of a disorder of renal tubular function. This disorder, although it is an expression of disordered enzyme action, is not even specific for cystine, and furthermore many other functions besides the enzyme action must be concerned in the tubular reabsorption of cystine; renal blood-flow, glomerular filtration, and the blood-level of cystine all affect the amount of cystine filtered, reabsorbed, and eventually appearing in the urine. The variable extent of glucose excretion in the inherited form of renal glycosuria may be explained in a similar manner.

We leave two chemical matters still unexplained. The excretion of the unidentified aminoacid 'fast-arginine' in one case (P. W.) is not explained, although we now believe it was probably an accidental finding unrelated to the cystinuria. We are also left in doubt whether ornithine was present in the fresh urine of our cystinuric patients, since we have not yet solved the technical difficulty of detecting this aminoacid in the presence of relatively large quantities of lysine, which has properties closely resembling it. We have found no evidence of the presence of cadaverine or putrescine. Under our experimental conditions they

both give typical ninhydrin colour reactions, and move to a position on the chromatogram almost identical with that occupied by 'fast-arginine'. We could not have failed to detect them if present in any appreciable quantity. When more cystinuric specimens have been examined it will be possible to say more definitely whether cadaverine and putrescine are ever passed in the urine of cystinuric subjects, as distinct from being formed, as we now suspect, in the stale urine as the result of the action of bacterial decarboxylases and other enzymes on the lysine, arginine, and perhaps ornithine which are present. We have no evidence in support of the view that the cystine is passed in the fresh urine in the form of a complex which only slowly decomposes on standing (Brand, Harris, and Biloon, 1930). So far as chromatographic behaviour is concerned, the cystine is the same in fresh urine and in urine which has stood for many days at room temperature, or which has been subjected to acid hydrolysis. The clinical condition present in the 15 cases described in this paper represents a definite and recognizable entity, breeding true to type and readily diagnosed by paper chromatography. Most of the published cases of cystinuria correspond to this type, and we propose that in future the diagnosis of 'cystinuria' be reserved for this condition. We would define the clinical condition of cystinuria as one characterized by the excessive and continuous excretion in the urine of cystine, lysine, and usually arginine, in the presence of normal plasma levels of these and of all the other common aminoacids—the condition being hereditary, present from birth, and consistent with normal health, apart from such complications as may arise from the occasional tendency to form renal calculi. We believe that this condition is due to a specific impairment of renal tubular function, and that the diagnosis should not be applied to cases in which an excessive excretion of cystine occurs either as part of a generalized aminoaciduria, or as a result of abnormal cystine levels in the blood, nor to any case in which there is serious systemic disease or deposition of cystine crystals in the tissues.

APPENDIX A

Brief Clinical Details of the Cases Studied

Seven of the eight cases with a history of renal symptoms (the exception is Mr. Sch., with whom we have lost touch) have been followed to a recent date (October 1950) both clinically and with frequent chromatographic urine analyses. We have not thought it advisable to do the same with the fully asymptomatic cases. The date is given at which the first specimen of urine from each patient was tested, so that the duration of the follow-up can be indicated. A genetic study has been made of most of these cases, and also of some other clinical conditions in which gross aminoaciduria occurs and usually includes an increased excretion of cystine as well as of many other aminoacids. This study will be reported by Dent and Harris (1951) in another journal. The pedigree numbers given below are those used in that report.

Mr. L. L. (Pedigree 3; II, 1). A taxi-driver aged 37 years. The first chromatographic urine analysis was in January 1946. His first attack of renal colic occurred at 17 years of age. He has had many similar attacks since, with occasional passage of small, smooth, greyish-white stones. Cystinuria was diagnosed when he was 21 years old. Nine years ago a stone was removed by operation from the left kidney, since when he has only very occasionally had renal symptoms. On examination he had hypertension (B.P. 215/140) with severe morning headaches, and had been admitted to hospital for this reason seven months previously. The urine contained a trace of protein. The blood-urea was 36 mg. per 100 ml., and the urea clearance 80 and 87 per cent. An intravenous pyelogram showed a longish irregular stone in the left kidney, with poor dye-concentration on that side. The right kidney functioned normally.

Mr. A. L. (Pedigree 6; I, 5). A commercial traveller aged 38 years. The first chromatographic urine analysis was in June 1946. He was well until he was 17 years old, when he woke up one night with severe left-sided renal colic; his twin brother, S. L., had an attack on the same night. An operation was then performed for the removal of stones from his left kidney. He had a further attack two years later, but on the whole remained well, although violent exertion such as playing football usually produced some temporary pain. Some stones were removed from his right kidney two years ago. He is now fairly well except for occasional attacks of gout. X-rays show stones to be present on both sides.

Mr. S. L. (Pedigree 6; I, 4). A business man aged 38 years. The first chromatographic urine analysis was in June 1946. He had no renal symptoms until he was 17 years of age, when he woke up one night with severe right-sided renal colic. (His twin brother A. L. had his first attack of renal colic on the same night, on the left side.) He was admitted to hospital, and stones were removed by operation from the right kidney; cystinuria was diagnosed from the result of the analysis. He was well for the next two years. and then had another attack of right-sided colic (his twin also having an attack at the same time on the left side), and a further operation was done for the removal of stones. He was well again until he was 27 years old, when he joined the army, and X-rays showed numerous stones in the right kidney. The left kidney was said to be normal. A right nephrectomy was done. When he was 32 years old a stone was removed from the left kidney. He has kept well since then, although he gets occasional aches in the left loin.

Mr. F. S. (Pedigree 7; II, 2). A photographer aged 35 years. This patient happens also to suffer from haemophilia. He has had no renal symptoms. His cystinuria was detected as the result of routine testing.

Mr. G. S. (Pedigree 5; II, 1). A clerk aged 36 years. The first chromatographic urine analysis was in November 1948. He was admitted to hospital two years ago complaining of an aching pain inside his right thigh which had been present for three weeks. Twelve hours before admission he had passed a considerable quantity of blood in his urine. He had never suffered before from such symptoms. The bleeding soon stopped, and the urine was then shown to contain a trace of protein. The blood-urea was 36 mg. per 100 ml., and the urea clearance 86 and 92 per cent. Concentration of the urine to s.g. 1,020, and its dilution to s.g. 1,006, were noted. An intravenous pyelogram showed the presence of a large stag-horn calculus on the left side, with some dye-concentration; the right kidney had a small stone, and concentrated the dye normally. He has had no further trouble since.

Mr. Sch. A male patient who has a history of renal calculi shown to be made of cystine, and who is one of a family several of whom are also cystinuric

subjects. Unfortunately we have been unable to obtain further details of this patient.

Mr. J. H. (Pedigree 4; III, 1). A fitter aged 23 years. The first chromatographic urine analysis was in September 1949. He had three severe attacks of right renal colic at 11, 19, and 22 years of age. Cystinuria was diagnosed on the first occasion from microscopy of the urine. He has never noticed the passage of stones in his urine. Apart from this he has been quite well, and does a heavy day's work without undue fatigue. When he was admitted to hospital for investigation seven months ago, X-rays showed no renal opacities; his urine reached a concentration of s.g. 1,029 and a dilution of s.g. 1,002. The blood-urea was 36 mg. per 100 ml. He continues to be healthy and well. This case is particularly interesting to us with respect to the causes predisposing to stone formation. Although the patient has never had any evidence of stones, his urine invariably deposits large numbers of typical cystine crystals, and indeed is the only urine in our present series which does this consistently.

Mrs. H. (Pedigree 4; II, 2). A housewife aged 51 years. The mother of Mr. J. H.; a healthy woman, with no history of urinary troubles. A straight X-ray of the abdomen shows no evidence of opaque calculi.

Mrs. R. P. (Pedigree 4; II, 7). A housewife aged 46 years. The aunt of Mr. J. H.; a healthy woman who has had no urinary symptoms.

Mr. W. M. (Pedigree 4; II, 5). A clerk aged 47 years. The maternal uncle of Mr. J. H.; a healthy man who has had no urinary symptoms.

Miss I. W. (Pedigree 1; III, 4). A printer aged 15 years. The first chromatographic urine analysis was in March 1950. She had had no renal trouble until two years ago, when she had an acute attack of right lumbar pain and dysuria, which was diagnosed as pyelitis. The attack rapidly cleared up, and she had no further trouble until a year ago, when she began to have aching and stabbing pains in the right loin; these became more severe until seven months ago, when she was admitted to hospital with severe right renal colic. She had recently passed red urine containing several small yellowish stones. X-rays showed very numerous stones in the right kidney, and one stone at the lower end of the left ureter. An intravenous pyelogram showed poor concentration of the dye by both kidneys, with gross hydronephrosis and hydroureter on the left side. The blood-urea was 33 mg. per 100 ml., and the urea clearance 26 and 38 per cent. After a month of low calcium and high fluid intake, with sufficient sodium bicarbonate to alkalinize the urine, she passed 284 stones in her urine, of a combined weight of 10·4 gm. The stones were shown to consist of almost pure cystine. A subsequent X-ray showed only one large stone in the right kidney, and the one already found in the left ureter. Both stones were removed by operation. When discharged she was well, her blood-urea was 30 mg. per 100 ml., and her urea clearance 46 and 61 per cent. She has had no further trouble in the last four months.

Mrs. P. R. (Pedigree 1; III, 2). A toy-packer aged 22 years. The first chromatographic urine analysis was in March 1948. She was well until five and a half years old, when she was admitted to hospital with frequency of micturition, dysuria, and left renal colic. A stone was removed from the bladder by litholapaxy, and another from the left kidney pelvis by operation. The stones were shown to consist of cystine. She was again well until she had an attack of pyelitis at nine years of age. This attack cleared up quickly, and she had no further trouble until she was 21 years old, when she had a bad attack of left renal colic. X-rays on this occasion showed a large stag-horn calculus in the right kidney, and multiple stones in the left. An intravenous pyelogram showed good dye-concentration on the right side, poor on the left. The blood-urea was

30 mg. per 100 ml., and the urea clearance 44 and 53 per cent. She has remained free of symptoms during the last few months.

Mr. F. W. (Pedigree 1; II, 2). Aged 47 years. The father of Miss I. W. and Mrs. P. R.; he has had no urinary symptoms.

Mrs. L. A. (Pedigree 1; II, 5). A housewife aged 42 years. The paternal aunt of Miss I. W. and Mrs. P. R.; a healthy woman, with no urinary symptoms.

Mr. A. W. A student aged 20 years. He has had no symptoms, and was discovered to have cystinuria by a routine urine test. There were no physical signs of disease on clinical examination.

APPENDIX B

Attempts to Identify 'Fast-Arginine' and to Detect Traces of Cadaverine and Putrescine in the Urine of Case P. W.

Since 'fast-arginine' moves on the chromatogram to a position close to that occupied by cadaverine and putrescine, an attempt was made to isolate it by steam distillation, under conditions already shown to be effective in trial runs using a solution of pure putrescine in water. A large sample of urine from Case P. W. was collected for the investigation in Winchester quart bottles, each containing 50 ml. of 15 per cent. (v/v) of concentrated HCl and 1 ml. of 10 per cent. alcoholic thymol. The bottles were collected every three days from the patient's home and stored at 4° C until 10 litres had been obtained. They were then mixed to make one sample. Five litres were then brought to pH 10 with 40 per cent. NaOH, and were boiled vigorously for 40 minutes. During this time a rapid current of steam containing a trace of capryl alcohol was bubbled through the boiling urine. The ensuing vapours were passed into 200 ml. of 2N HCl. The acid solution, assumed to have trapped any volatile bases, was evaporated to dryness, and the residue (chiefly, if not entirely, NH_4Cl) dissolved in 8 ml. of distilled water. Chromatographic analysis of 25 μl. lots of this solution failed to show the presence of any cadaverine or putrescine. We could readily detect 5 μg. of either substance by this method. We presume therefore that there was much less than 1 mg. in the 8 ml. of final distillate from the 5 litres of urine. Even if only a small proportion of the cadaverine or putrescine originally present had distilled off, which is unlikely, the maximum amount that could have been present is still very small. The 'fast-arginine' spot must therefore be mainly due to some substance other than cadaverine or putrescine. From the strength of the ninhydrin reaction, the urine probably contained about 500 mg. of 'fast-arginine' in the five litres. Having failed to isolate the compound in this way, we investigated in the whole urine a few further properties which are recorded below.

Acid hydrolysis. The spot was still present in full strength when the urine had been hydrolysed as described above.

Alkaline hydrolysis. A specimen of urine was heated in a sealed tube at 100° C for 21 hours with an equal volume of 40 per cent. NaOH. It was desalted, and aliquots equivalent to 125 and 780 μl. of original urine were analysed chromatographically. No 'fast-arginine' had survived. It is therefore destroyed in this process.

H_2O_2 treatment. Twenty-five μl. of urine treated with 5 μl. of H_2O_2 and 5 μl. of 0·1 per cent. ammonium molybdate showed the usual quantity of 'fast-arginine', and no new spots on chromatography. It is therefore unlikely to contain oxidizable sulphur in the molecule. The spot seen in the same position in the plasma chromatograms of P. W. was likewise unchanged after oxidation.

Acid chromatogram (as described by Dent, 1948b). The rate of movement of the 'fast-arginine' in the phenol solvent was considerably slowed when run under acid conditions. It is therefore probably basic in character.

We wish to thank Mr. F. J. F. Barrington, Dr. C. L. Cope, Dr. N. Malleson, and Dr. W. Q. Wolfson for putting us in touch with known cases of cystinuria, and Dr. H. Harris, who through genetic studies (Dent and Harris, 1951) of our patients, discovered most of the affected relatives. We are also indebted to Dr. W. Cuthbertson for the microbiological assays.

Summary

1. Fifteen patients with cystinuria have been studied. All were adults enjoying good general health, and all but two either had had, or were close relatives of patients with, renal colic or stones. The urine in every case gave a strongly positive cyanide-nitroprusside reaction.

2. The urine in all cases was analysed for aminoacids by paper chromatography. Apart from the cystine a grossly excessive excretion of lysine was always found, arginine was nearly always increased, and 'fast-arginine' was found intermittently in one case. Cadaverine and putrescine were not detected, although the methods used were suitable for the purpose.

3. In a few cases the urine was repeatedly examined at intervals for periods up to four years. The pattern of excretion of aminoacids, although slightly different from case to case, was fairly constant in any one patient and in his affected relatives.

4. The plasma was analysed for aminoacids in seven cases. So far as could be judged by matching the strengths of the ninhydrin colours of the spots, the concentrations of all the detectable aminoacids were normal, except in one patient whose plasma sometimes contained an abnormal concentration of 'fast-arginine'. The cystine concentrations in two cases were also found to be normal when determined by microbiological assay.

5. We believe that the immediate cause of the grossly excessive excretion of cystine, lysine, and arginine in the urine is a low renal threshold, presumably due to a defective capacity of the renal tubules to reabsorb these substances. These three aminoacids may be handled in the same way by the tubule owing to their possession of a general structural resemblance to each other. There does not appear, in the present state of our knowledge, to be any metabolic relation between them.

6. We have found no evidence that there is any error of aminoacid metabolism in the body tissues, apart from the renal tubules, in these cases of cystinuria.

7. Other conditions in which there is an excessive excretion of cystine into the urine, and which are usually associated with serious organic disease, are considered to be entirely separate from the condition described. Such diseases—the Fanconi syndrome, hepatolenticular degeneration, and probably others—show what is better described as a gross aminoaciduria, that is, an excessive

excretion of nearly all the common acidic, neutral, and basic aminoacids. These diseases are easily distinguishable by paper chromatographic analysis of the urine.

8. We propose that the diagnosis of 'cystinuria' should be limited in future to cases of the type studied in the present paper, that is to a condition presumed to be present from birth, and characterized by the excretion in the urine of large quantities of cystine (about 1 gm. in 24 hours in the adult), lysine, and usually arginine. The condition is often present in the patient's relatives, and may result in the formation of stones composed almost entirely of cystine. Apart from the possibility of kidney damage resulting from stone formation, the patients enjoy good health, and are clinically indistinguishable from normal. Cases also occur in which the excretion of cystine is intermediate between the normal and 'cystinuric' levels.

9. We can see no aetiological connexion between cystinuria as described here and the condition known as cystinosis, in which cystine is deposited in the body tissues, and in which there is severe organic disease and an invariably fatal outcome at an early age.

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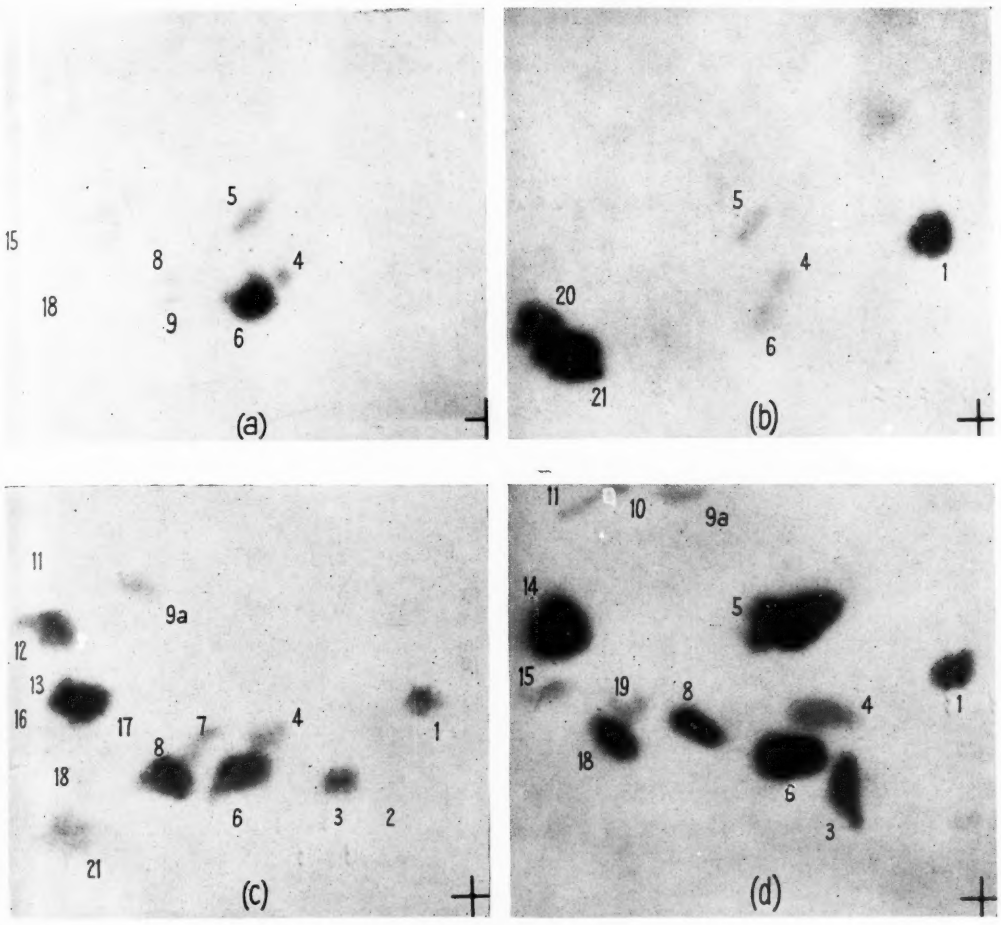

FIG. 2. Photographs of chromatograms of urine

In each case the volume of urine which contains 250μg. of nitrogen has been taken for analysis. The urine was placed on the pencilled cross, and phenol was run from right to left as first solvent, followed by collidine-lutidine in an upward direction. The spots show the aminoacids in their final positions as revealed by the ninhydrin reaction: 1, cystine (as cysteic acid); 2, aspartic acid; 3, glutamic acid; 4, serine; 5, taurine; 6, glycine; 7, threonine; 8, alanine; 9, glutamine; 9a, tyrosine; 10, tryptophane; 11, phenylalanine; 12, leucine or isoleucine, or both; 13, valine; 14, ethanolamine; 15, methylhistidine; 16, proline; 17, α-amino-*n*-butyric acid; 18, β-aminoisobutyric acid (Crumpler, Dent, Harris, and Westall, 1951); 19, histidine; 20, arginine; 21, lysine.

(*a*) Normal urine. The pattern varies slightly from person to person, but this example is typical.

(*b*) Cystinuric urine from one of the cases described in the text. The only definitely abnormal features are the grossly excessive concentrations of cystine (1), lysine (21), and arginine (20).

(*c*) Urine from a case of the Fanconi syndrome. The cystine (1) is only one of very many aminoacids excreted in grossly abnormal concentration.

(*d*) Urine from a case of advanced cirrhosis of the liver. The special point of interest is that the cystine (1) excretion was associated with a raised plasma cystine level, without an abnormal urinary excretion of lysine (21). These may be the only abnormalities found in aminoacid metabolism in cirrhosis, or they may be associated, as here, with abnormal excretion of other aminoacids such as taurine (5), ethanolamine (14), and β-aminoisobutyric acid (18). (Taken from Dent and Walshe, 1950, and further unpublished work.)

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POTASSIUM DEFICIENCY IN ULCERATIVE COLITIS[1]

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THE connexion between low levels of the serum-potassium and muscular weakness was first established in cases of familial periodic paralysis (Aitken, Allott, Castleden, and Walker, 1937). Since then the occurrence of a low level of serum-potassium, associated with muscular weakness, has indicated the presence of a potassium deficiency in a number of conditions: Cushing's syndrome (McQuarrie, Johnson, and Ziegler, 1937), Addison's disease where there has been overdosage with desoxycorticosterone acetate (Thorn and Firor, 1940), chronic nephritis (Brown, Currens, and Marchand, 1944), diabetes mellitus (Holler, 1946), intestinal obstruction with vomiting (Bellet, Nadler, Gazes, and Lanning, 1949), and various conditions treated with cortisone (Sprague, Power, Mason, Albert, Mathieson, Hench, Kendall, Slocumb, and Polley, 1950) or *p*-aminosalicylic acid (Cayley, 1950). Some types of diarrhoea are also known to produce potassium deficiency: infantile diarrhoea (Darrow, 1946), tropical sprue, idiopathic steatorrhoea, and secondary steatorrhoea (Harrison, Tompsett, and Barr, 1943; Engel, Martin, and Taylor, 1949; Lubran and McAllen, 1951). The only reference to potassium deficiency in ulcerative colitis which we have been able to trace is that of Gardner, MacLachlan, Terry, McArthur, and Butler (1949) who mentioned incidentally that they had seen two such cases. During the past two years we have found evidence of potassium deficiency in four out of 30 consecutive cases of ulcerative colitis. The findings in these four cases are recorded in the present paper.

Case Reports

Case 1. A single woman, aged 44 years. She developed ulcerative colitis when 21 years old, and had exacerbations at 22 and 42 years of age. When she was 34 years old a right nephrectomy was carried out for a renal abscess. In subsequent years she had several attacks of *Bact. coli* urinary infection. In September 1948 she was admitted to hospital, having had a third exacerbation of the ulcerative colitis. She improved a little after six weeks' treatment during which penicillin, sulphonamides, kaolin, and vitamins were given. After her discharge the diarrhoea became more severe, and she was readmitted on November 14, 1948. On examination she was wasted, but there were no other abnormal findings apart from tenderness over the region of the transverse colon. The blood-pressure was 120/85. The patient was passing 10 to 12 fluid stools daily which contained blood and mucus.

[1] Received December 12, 1950.

Investigations. The blood count showed haemoglobin 101 per cent. (14·8 gm. per 100 ml.), white cells 13,900 per c.mm. (neutrophils 84 per cent., lymphocytes 10 per cent., monocytes 5 per cent., eosinophils 1 per cent.). The stools contained no pathogenic organisms, cysts, amoebae, or parasites. Sigmoidoscopy showed changes typical of severe ulcerative colitis, and the appearance of a barium enema was consistent with this condition. A barium meal and an X-ray of the chest were normal. An oral glucose-tolerance test was normal. A three-day fat balance (210 gm. fat intake) showed 89 per cent. absorption. The urine was normal, and cultures were sterile. The blood-urea was 25 mg. per 100 ml. The urea clearance (corrected to 1·73 sq. metres body-surface) was 94 per cent. of the average maximum normal. An intravenous pyelogram showed a normal left kidney; the right kidney was absent.

Progress. The patient was treated as on her first admission, but the diarrhoea remained unchecked. By the end of four weeks she had become generally weak and clinically dehydrated. At this time (December 16) the blood showed the following values per 100 ml.: sodium 283 mg. (123 mEq per litre), potassium 14·3 mg. (3·67 mEq per litre), chlorides 515 mg. (88 mEq per litre),[2] alkali reserve 79 ml. CO_2 (35·5 mEq bicarbonate per litre), urea 103 mg. Although the dehydration was corrected by oral and intravenous fluids for the next few days, the patient's condition continued to deteriorate until she presented a striking picture of muscular weakness, and death appeared imminent. She lay still in bed with her head lolling and eyelids drooping. Her fingers could not grasp a cup, nor could she even raise her arms off the bed-clothes. The only voluntary movement in the lower limbs was of the toes and feet. The muscles of the limbs were hypotonic, and the deep tendon-reflexes were diminished. There were no paraesthesiae or other sensory disturbances. The serum values per 100 ml. were now (December 21): sodium 304 mg. (132 mEq per litre), potassium 11·1 mg. (2·85 mEq per litre), chlorides 590 mg. (101 mEq per litre). It was clear that the patient was in a state of severe potassium deficiency, and she was therefore given potassium chloride, 4 gm. three times a day by mouth. No other treatment was given, but within 24 hours her muscular weakness had lessened considerably, and after three days her strength had returned to normal. Her general condition was now much improved, although the severity of the diarrhoea remained unchanged. On December 29 the blood chemistry values per 100 ml. were: sodium 310 mg. (135 mEq per litre), potassium 20·7 mg. (5·31 mEq per litre), chlorides 590 mg. (101 mEq per litre). After two weeks' administration the potassium therapy was stopped, and the patient was well enough to be discharged for out-patient observation. The diarrhoea, however, continued little changed. Three weeks later (January 26, 1949) the serum-potassium had fallen to 6·3 mg. per 100 ml. (1·61 mEq per litre), and some degree of weakness had returned. Potassium chloride, 4 gm. three times a day, was given again, and the weakness disappeared. After a further 21 days potassium therapy was discontinued, but once more weakness returned in about three weeks. The serum-potassium now (March 21) was 8·0 mg. per 100 ml. (2·05 mEq per litre). The weakness was again relieved by potassium chloride. There was no history of familial periodic paralysis in the patient's family to account for the recurrent attacks of weakness. The effect of prostigmine was observed on several occasions. It was found that 2·5 mg. by injection produced no change in the muscular weakness. During the remainder of 1949 the diarrhoea continued with little variation, and the patient required 8 to 10 gm. of potassium chloride daily in order to prevent a return of muscular weakness. This dose kept the fasting level of serum-potassium above 11·0 mg. per 100 ml. (2·82 mEq per

[2] Serum-chlorides are expressed as mg. NaCl per 100 ml. throughout.

litre). It was found that the patient obtained the greatest benefit subjectively when the daily dose of potassium chloride was increased to the limit of her tolerance. This dose proved to be 24 gm. of the salt divided into four-hourly portions. Early in 1950 the frequency of the stools decreased to one, two, or three a day. The serum-potassium rose to 16·0 mg. per 100 ml. (4·10 mEq per litre), and remained at this level even after potassium therapy was discontinued. When the serum-potassium was low, the electrocardiogram in this case consistently showed abnormalities in the ST segment, T wave, and U wave. These changes have been reported in detail elsewhere (McAllen, 1951).

TABLE I

Daily Potassium and Sodium Balances in Case 1 (Balance A)

The patient was on a standard diet for the three days preceding the balance and throughout the balance experiment itself. During the period marked * 16 gm. potassium chloride (8·4 gm. potassium) were given. The normal range of serum-potassium is 16 to 22 mg. per 100 ml. (Bodansky, 1938). Normally the bulk of the ingested sodium and potassium appears in the urine, and less than 0·5 gm. of each appears daily in the faeces (Hawk, Oser, and Summerson, 1947).

	Daily intake in gm.		*Daily output in gm.*				*Balance*		*Serum (mg./100 ml.)*		
			Urine		*Faeces*						
Date	*K*	*Na*	*K*	*Na*	*K*	*Na*	*K*	*Na*	*K*	*Na*	*Cl*
March											
15/16	1·6	11·2	0·49	0·42	1·30	2·45	−0·2	+8·3	9·6	307	630
16/17	1·6	11·2	0·44	0·42	1·95	3·70	−0·8	+7·1			
17/18	1·6	11·2	0·33	0·37	2·07	3·53	−0·8	+7·3	10·3	298	580
18/19*	9·9	11·2	0·72	0·39	2·30	3·50	+6·9	+7·3	9·3	323	560
19/20	1·6	11·2	0·35	0·18	1·55	2·16	−0·3	+8·9	10·7	328	560
20/21	1·6	11·2	0·42	0·14	1·01	2·62	+0·2	+8·4			
21/22	1·6	11·2	0·36	0·14	0·92	1·35	+0·3	+9·7	8·0	334	570

TABLE II

Daily Potassium and Sodium Balances in Case 1 (Balance B)

The procedure was the same as in Balance A. During the periods marked * 24 gm. potassium chloride (12·6 gm. potassium) were given daily.

	Daily intake in gm.		*Daily output in gm.*				*Balance*		*Serum (mg./100 ml.)*		
			Urine		*Faeces*						
Date	*K*	*Na*	*K*	*Na*	*K*	*Na*	*K*	*Na*	*K*	*Na*	*Cl*
Nov.											
8/9*	14·5	4·0	0·44	Nil	1·65	3·37	+12·4	+0·6	13·4	312	440
9/10*	14·4	3·9	0·42	,,	1·95	4·67	+12·0	−0·8			
10/11*	14·6	3·9	0·75	,,	2·30	3·87	+11·6	0·0	9·3	316	
11/12*	14·3	3·9	0·69	,,	2·54	5·12	+11·1	−1·2			
12/13*	14·6	3·9	0·53	,,	2·39	5·20	+11·7	−1·3			
13/14*	14·6	3·8	0·52	,,	2·41	5·33	+11·7	−1·5			
14/15	2·0	3·9	0·50	,,	2·12	4·02	−0·6	−0·1	10·9	288	430
17/18	2·0	3·9	0·94	,,	2·14	4·32	−1·1	−0·4	8·6	282	445
20/21	1·8	3·9	0·80	,,	2·25	5·38	−1·3	−1·5	9·4	303	450
23/24	1·9	4·0	0·80	,,	2·12	5·50	−1·0	−1·5	11·9	294	475
27/28	2·0	3·8	0·83	,,	2·54	6·09	−1·4	−2·3	11·1	270	460

Metabolic studies. Combined potassium and sodium balances were carried out on two occasions eight months apart (Tables I and II) during the prolonged exacerbation of the ulcerative colitis. In Balance A the intake of potassium was low but, as the patient had 'salt hunger', the intake of sodium was high. The figures show that the potassium loss was abnormally high in the faeces and

low in the urine, a negative balance resulting until a large dose of potassium chloride was given by mouth. This dose was nearly all retained, and the balance became positive. Sodium loss was also remarkably high in the faeces and low in the urine, but the balance of sodium was positive throughout. In Balance B the intake of potassium was high in the first part, but low in the second part of the test. Throughout the test potassium was lost in the faeces in large amounts, and in the urine in small amounts, as in Balance A. The potassium balance was

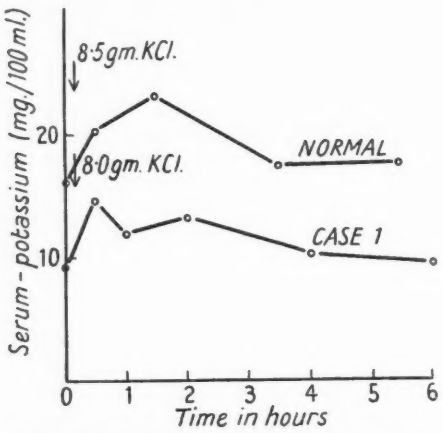

FIG. 1. Oral potassium-tolerance curve in Case 1. The test dose of potassium chloride was dissolved in 700 ml. of water. A similar test was carried out on a comparable normal subject.

strikingly positive during the first part, and was negative during the second part of the test. The values of the faecal and urinary excretion showed little change throughout, despite the marked difference in potassium intake. The sodium intake was low throughout the test, and the balance was mainly negative. The sodium loss was high in the faeces and very low in the urine, as in Balance A. An oral potassium-tolerance test was carried out during a severe phase of the disease. A dose of 8 gm. of potassium chloride in 700 ml. of water was given. The resultant curve (Fig. 1) was normal, being in keeping with the curves described by Zwemer and Truszkowski (1936), Keith, Osterberg, and Burchell (1942), and Keith and Osterberg (1946), and with our own observations. The serum-potassium level rose to a maximum after 30 minutes, and slowly returned to the starting level during the next six hours. An oral sodium-tolerance test with 8 gm. of sodium chloride produced no change in the serum level of sodium, and a slight fall in that of potassium (Fig. 2).

Case 2 was a married woman, aged 39 years, who had developed a severe form of ulcerative colitis three years previously. She was thin, but physical examination was otherwise normal. During an acute phase (June to September 1949) in which she passed six to thirteen fluid stools a day, the serum-potassium fell from 16·5 mg. per 100 ml. (4·23 mEq per litre) to 12·9 mg. per 100 ml. (3·31 mEq per litre) in four months. The serum-sodium rose from 293 mg. per 100 ml. (127 mEq per litre) at the beginning of the same period to 343 mg. per 100 ml. (149 mEq per litre) at the end. The serum-chlorides remained constant at

530 to 540 mg. per 100 ml. (91 to 92 mEq per litre). The condition then improved, and four months later, when the patient was passing four semi-solid stools a day, the values per 100 ml. of serum were: potassium 21·8 mg. (5·59 mEq per litre), sodium 318 mg. (138 mEq per litre), chlorides 590 mg. (101 mEq per litre). No muscular weakness was associated with the low serum-potassium levels. The electrocardiogram was normal when the serum-potassium level was within normal limits, but showed a decrease in the voltage of the T wave when the potassium was 12·9 mg. per 100 ml.

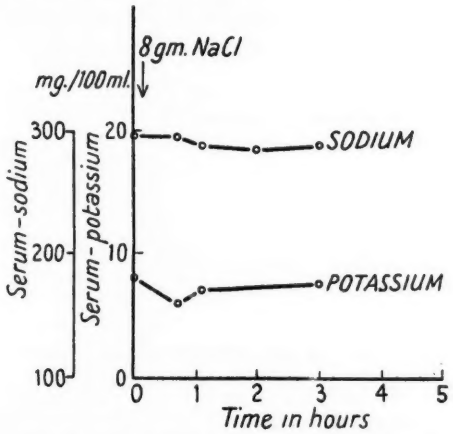

FIG. 2. Oral sodium-tolerance curve in Case 1. The test dose of sodium chloride was dissolved in 700 ml. of water. The changes in potassium concentration are also shown.

Case 3 was a married woman, aged 39 years, who had suffered from ulcerative colitis for one year. She was admitted to hospital on September 19, 1949, during a severe exacerbation in which she was passing more than 10 liquid stools a day. One of her presenting symptoms was muscular weakness, which she had first noticed about six weeks previously. The weakness had first affected the legs, and by the time she was in hospital had spread to the arms and trunk. She was unable to sit up in bed, and could only feed herself with difficulty. The deep tendon-reflexes were normal, and sensation was unimpaired. She remained very ill, and died after six weeks from bowel haemorrhage and multiple perforations. During her last four weeks the serum-potassium was found on two occasions to be 12·4 mg. per 100 ml. (3·18 mEq per litre) and 12·7 mg. per 100 ml. (3·25 mEq per litre) respectively. On the second occasion the serum-sodium was 327 mg. per 100 ml. (142 mEq per litre) and chlorides 470 mg. per 100 ml. (80 mEq per litre).

Case 4. A single girl, aged 21 years, had a history of ulcerative colitis persisting since the age of two and a half years. In June 1950 she was admitted to hospital with abdominal pain of moderate severity. She was passing eight to fourteen fluid stools, containing blood and mucus, daily. A slightly tender mass was found in the right side of the abdomen. The clinical diagnosis was a localized leak into the peritoneum from the diseased colon. The serum electrolyte levels per 100 ml. were: potassium 23·3 mg. (5·97 mEq per litre), sodium 337 mg.

(147 mEq per litre), chlorides 550 mg. (94 mEq per litre). She was discharged after four weeks, free from pain but otherwise unchanged. After several weeks there was a return of the abdominal pain, and the frequency of the stools increased to 10 to 20 a day. She was readmitted on August 19, 1950. On examination the patient was thin, and looked ill. The temperature was 101° F., and the pulse-rate 100. The mass in the abdomen was unchanged. There were no other abnormal findings on physical examination. The blood-pressure was 115/80. During the next few days the patient gradually developed a marked hypotonic muscular weakness affecting the arms, legs, and trunk. There was also a slight drooping of the eyelids, and she complained of difficulty in swallowing. The degree of weakness was such that she was unable to lift her head from the pillow, or to raise her arms more than a few inches from the bed. The proximal muscles of the arms and legs appeared to be more affected than the distal muscles. The deep tendon-reflexes were all diminished. There were no sensory disturbances. The blood chemistry values per 100 ml. were: potassium 14·7 mg. (3·76 mEq per litre), sodium 338 mg. (147 mEq per litre), chlorides 500 mg. (85 mEq per litre). Three days later the weakness was unchanged, and a further examination showed potassium 12·5 mg. per 100 ml. (3·22 mEq per litre), sodium 300 mg. per 100 ml. (130 mEq per litre), and chlorides 500 mg. per 100 ml. (85 mEq per litre). When 2 gm. of potassium chloride were given by mouth each hour for four hours, a definite lessening in the degree of weakness resulted. Electrocardiograms were taken at the times when the blood chemistry was determined, and showed no abnormality when the serum-potassium was normal. There was a decrease in the amplitude of the T wave when the serum-potassium was 14·7 mg. and 12·5 mg. per 100 ml. The patient gave the interesting history that for many years she had had 'salt hunger' and had taken an unusually large amount of salt with every meal.

Discussion

The state of potassium deficiency may be recognized by a generalized hypotonic muscular weakness in the arms, legs, and trunk, the site of maximum weakness varying from case to case. The weakness may sometimes progress to a flaccid paralysis. The deep tendon-reflexes are usually diminished or absent, and paraesthesiae may occur in the limbs. Occasionally there is difficulty in swallowing. Involvement of the respiratory muscles may result in shallow, rapid breathing, or even in death from respiratory paralysis (Holler, 1946; Nicholson and Branning, 1947). The level of serum-potassium is found to be abnormally low, and the muscular weakness can always be relieved by the administration of adequate amounts of potassium. Abnormalities may occur in the electrocardiogram, their degree being related to the level of the serum-potassium. These abnormalities may often be found before marked muscular weakness has appeared, and the electrocardiogram may thus be an early guide to diagnosis. There may be a decrease in amplitude, or an inversion, of the T wave, a depression of the ST segment, and the appearance of a large U wave. It is stated that the QT interval is often prolonged, but in the opinion of one of the authors the frequency of this occurrence has been over-estimated (McAllen, 1951). All these changes can be corrected rapidly by potassium therapy. It is thought that potassium deficiency may occasionally produce other cardiological effects. Those

described are a loud precordial systolic murmur, dilatation of the heart, and a raised venous pressure in the neck (Frenkel, Groen, and Willebrands, 1947; Gamble, Wiese, and Hansen, 1948). Examination of the blood chemistry shows that the low level of serum-potassium is commonly associated with low serum-chloride and high serum-bicarbonate levels (Darrow, Schwartz, Iannucci, and Coville, 1948). It is sometimes possible to confirm the diagnosis of potassium deficiency by means of a potassium balance. During the untreated state of deficiency there is a markedly negative balance, and during the period of recovery there is a considerable retention of potassium. Potassium deficiency with muscular weakness may be difficult to differentiate from familial periodic paralysis, myasthenia gravis, and some cases of thyrotoxicosis, in all of which conditions a similar type of muscular weakness may arise, and may also be lessened by the administration of potassium. In familial periodic paralysis, however, there is usually a clear hereditary history, and the attacks are sudden in onset and recurrent (Gass, Cherkasky, and Savitsky, 1948). The weakness of myasthenia gravis can be relieved by prostigmine, but in our experience prostigmine is without effect in potassium deficiency. In thyrotoxicosis the specific treatment of this condition will relieve the associated muscular weakness (Hildebrand and Kepler, 1941; Seed, 1947). Mild grades of potassium deficiency may frequently be overlooked, the associated muscular weakness being attributed to an underlying chronic disease.

In ulcerative colitis little attention has been paid to the loss of electrolytes in the faeces, although faecal electrolyte loss has long been known to occur in other diseases associated with a profuse diarrhoea. Darrow (1946) quotes Schmidt (1850) as first describing the marked loss of sodium and potassium in the acute diarrhoea of cholera and dysentery. Numerous authors have drawn attention to the loss of sodium and potassium in infantile diarrhoea. Welch, Adams, and Wakefield (1937) described metabolic studies in three patients suffering from ulcerative colitis, none of whom, however, had a lowered serum-potassium or muscular weakness. These cases showed an average loss in the stools of about 1 gm. of potassium daily. The present paper shows that in Case 1 a persistent large loss of potassium in the stools from ulcerative colitis resulted in the characteristic changes of severe potassium deficiency. In Cases 3 and 4, during periods of profuse diarrhoea from the same disease, there also occurred muscular weakness and low levels of serum-potassium. In Case 1 other possible causes of the faecal loss of potassium, such as an infective diarrhoea, sprue, idiopathic steatorrhoea, and secondary steatorrhoea, were excluded by the investigations. In this patient it is possible to arrive at the probable mechanism of potassium loss. The oral potassium test (Fig. 1), carried out in a severe phase, showed rapid absorption of the degree found in normal people. The glucose-tolerance test and the fat balance also showed normal absorption. It therefore seems unlikely that the increased faecal loss of potassium was due to defective absorption. There is, however, a close relationship between the volume of fluid passed in the stools and the amounts of potassium and sodium lost (Table III). The excessive amounts of water and electrolytes in the stools can be explained by an

increased permeability of the diseased colon, allowing much fluid to diffuse into its lumen from the blood-stream. The concentration of electrolytes in the colon tends to approach that of an isotonic solution, and the amount of electrolytes depends upon the volume of fluid passed. In normal subjects the fluid content of the stools is low compared with the urinary volume, and consequently the loss of electrolytes in the stools is low compared with the loss in the urine; but in Case 1 the volume of the stools was from one to three times the volume of the urine excreted each day, and the result was a high loss of potassium and sodium in the stools, and a low loss in the urine. As Table III shows, there is a

TABLE III

Daily Excretion of Potassium and Sodium in relation to Faecal Volume in Case 1

Owing to the fluidity of the stools it was possible to measure the faeces by volume. The mean value of the concentration of Na+K in mEq per litre was for Balance A 101·0, and for Balance B 111·7. The mean for both balances taken together was 107·5.

Date	*Daily volume of faeces (ml.)*	*Daily output in mEq*			*Concentration in mEq/litre*		
		K	*Na*	*K+Na*	*K*	*Na*	*K+Na*
Balance A:							
March							
15/16	1,480	33·4	106	139	22·7	71·6	94·3
16/17	1,960	50·0	161	211	25·6	82·1	107·7
17/18	1,990	53·1	154	207	26·7	77·4	104·1
18/19	2,220	59·0	152	211	26·6	68·5	95·1
19/20	1,200	38·8	94	133	32·3	78·3	110·6
20/21	1,160	25·9	114	140	22·3	98·3	120·6
21/22	1,105	23·6	59	83	21·4	53·4	74·8
Balance B:							
Nov.							
8/9	2,140	54·4	175	229	25·4	81·8	107·2
9/10	2,160	54·8	188	243	25·4	87·0	112·4
10/11	2,600	57·6	234	292	22·2	90·0	112·2
11/12	2,500	54·4	239	293	21·8	95·6	117·4
12/13	2,900	65·1	265	330	22·4	91·4	113·8
13/14	1,685	42·3	146	188	25·1	87·8	112·9
14/15	2,300	50·0	204	254	21·7	88·7	110·4
17/18	2,150	59·0	169	228	27·5	78·6	106·1
20/21	2,560	65·1	223	288	25·4	87·1	112·5
23/24	2,600	61·3	226	287	23·6	86·9	110·5
27/28	2,600	61·8	232	294	23·8	89·2	113·0

rough parallelism between the excretion of each of the two individual electrolytes and the volume of stool each day, but there is a much closer linear relationship between the sum of potassium and sodium concentrations and the stool volume. The mean concentration of these electrolytes in the faeces is 107·5 mEq per litre, which is 70 per cent. isotonic. A similar calculation applied to the data of Welch, Adams, and Wakefield (1937) gives a value for the concentration of electrolytes of 150 mEq per litre, which is isotonic. The figures are only roughly comparable, as the data of these authors are expressed in terms of weight of water in the stool, and our data in terms of fluid volume of the stool.

But both sets of data lend strong support to the idea that the main determinant of the degree of electrolyte loss is the volume of the stools. In Case 1, whatever the tissue concentrations, there must have been a steady drain of electrolytes into the colon. The kidney, through its ability to conserve sodium, was able to compensate somewhat for the sodium loss. It seems that there is no great degree of conservation of potassium by the kidney (Tarail and Elkinton, 1949), and thus the loss of this electrolyte in the faeces gradually led to tissue depletion, which was prevented only by a greatly increased intake of potassium. In ulcerative colitis it is possible that an excess of faecal potassium might be derived from desquamated cells, pus, and blood. Welch, Adams, and Wakefield (1937) showed that there was a marked increase of faecal nitrogen in their cases (up to 10 gm. daily), and they therefore attributed the raised faecal potassium (1 gm. daily) to cellular debris. This explanation is unlikely to be correct. In the tissues 1·0 gm. of nitrogen corresponds on the average to 0·04 gm. of potassium (Bodansky, 1938) and therefore, in their cases, the excretion of 10 gm. of faecal nitrogen would correspond only to 0·4 gm. of potassium. Further, the actual amount of potassium directly attributable to cellular cytoplasm must be much less than this, as a considerable part of the faecal nitrogen is derived from other sources which contribute less potassium than cellular cytoplasm, namely intestinal secretions, endogenous nitrogen metabolism, bacteria, and ammonia. In Case 1 of the present series the average daily excretion of nitrogen, measured in a severe phase, was 5·0 gm., and it does not seem likely that cellular debris could have provided much of the faecal potassium, especially in view of the fact that the solid content of the stools seldom exceeded 4 per cent. of their total weight.

It is of interest to note the considerable amount of potassium retained in Case 1 during potassium therapy. In Balance B during six days there was retention of about 70 gm. of potassium, yet the serum-potassium level fell. This remarkable degree of retention is a measure of the severity of the potassium deficiency which was present. Similar occurrences have been reported in other cases of potassium deficiency. Tarail and Elkinton (1949) showed that, in potassium deficiency associated with gastro-intestinal disturbances, considerable retention of potassium results from potassium therapy. Howard and Carey (1949), in a case of diabetic acidosis with a low serum-potassium, reported the retention of about 80 per cent. of an intravenous infusion of 35 gm. of potassium chloride (18·4 gm. of potassium) given in 18 hours. In Case 1 there was also a marked loss of sodium in the stools, and this was reflected in the low serum-sodium levels. In Cases 2 and 4 there were again low serum-sodium levels. It is of interest that Cases 1 and 4 had 'salt hunger', which suggested low stores of sodium, and perhaps of potassium, in the tissues.

Since severe potassium deficiency may cause death from paralysis of the respiratory muscles, or possibly from heart failure, it is clearly important to restore the reserves of the body as quickly as possible by the administration of potassium salts. The dosage is an individual problem in each case, and large doses are usually required. Potassium chloride may be given intravenously in

isotonic solution (1·14 per cent.); but there is a risk of potassium intoxication if the serum level rises too rapidly, and this route of administration should therefore be reserved for cases in which life is immediately threatened. The danger lies in the production of abnormalities of conduction in the heart, which may progress to cardiac arrest. This effect is likely to occur if the extracellular concentration of potassium rises to more than twice its normal value. It is the rapid administration of potassium that is dangerous, rather than the giving of a large total dose, and intravenous potassium should therefore be given slowly. Darrow (1948) estimated that, where renal function is normal, a safe dose to give in 24 hours is 0·26 gm. of potassium chloride per kg. of body-weight. This dose should be given by intravenous drip in not less than four hours, and preferably in more than eight hours. He suggested that the danger of toxicity may be reduced by combining the intravenous potassium with sodium chloride and glucose. Frequent electrocardiography may be used to control treatment, for the earliest evidence of toxicity is to be found in the electrocardiogram. The first abnormality to develop is a tall narrow T wave. As the level of serum-potassium rises the ST segment becomes depressed, and there is a decrease in the amplitude of the P wave, progressing to auricular standstill. At the same time defects of conduction occur: partial auriculo-ventricular block, intraventricular block, and prolongation of the QT interval. Later there is ventricular arrhythmia, and eventually ventricular standstill (Keith, Burchell, and Baggenstoss, 1944; Finch, Sawyer, and Flynn, 1946). In most cases potassium chloride can be given by mouth, and to avoid an emetic action it is best given in isotonic solution. It is safe to start administration with doses of 0·06 gm. of potassium chloride per kg. of body-weight (approximately 4 gm. of potassium chloride for the average adult) every one or two hours. In other cases similar quantities of an isotonic solution can be given by subcutaneous drip. This method is without the dangers of intravenous administration, unless hyaluronidase is used to increase the rate of absorption. Potassium therapy by either route should be continued in the same doses until the signs of potassium deficiency have disappeared, but it is advisable in the average adult not to exceed 24 gm. of potassium chloride during each 24-hour period. Further dosage must be determined empirically. The electrocardiographic changes are also of use in controlling dosage by oral and subcutaneous routes. In cases of ulcerative colitis, once the state of potassium deficiency has been corrected, a guide to further therapy is given by the volume of the stools, about 2 gm. of potassium chloride being required to make good the potassium loss in one litre of fluid faeces.

The four cases with evidence of potassium deficiency reported in this paper occurred in a series of 30 consecutive cases of ulcerative colitis. This incidence suggests that potassium deficiency in ulcerative colitis is more common than has been recognized.

Experimental Methods

In conducting the balances the potassium and sodium contents of the diet were calculated from the Tables of McCance and Widdowson (1940). The

potassium and sodium content of the stools and urine was determined in the wet specimens, after thorough mixing by six hours' mechanical stirring, by a method essentially that of Milton, Hoskins, and Jackman (1944). Nitrogen was determined by the standard Kjeldahl technique. Serum-potassium was estimated by the method of Jacobs and Hoffman (1931), serum-sodium by the method of Noyons (1939), and serum-chlorides by the method of Saifer and Hughes (1939). All determinations were carried out in duplicate. Blood specimens were collected before breakfast at a fixed time. The times of administration of potassium chloride were such that at least four hours elapsed between a dose and the taking of a blood specimen.

We wish to express our thanks to Dr. N. F. Coghill for allowing us to study the cases under his care, and to Dr. M. M. Deane for permission to include Case 3. We are indebted to Mr. R. J. Hall for carrying out the numerous biochemical determinations.

Summary

1. Four cases of ulcerative colitis with evidence of potassium deficiency are described.

2. A detailed study of one case showed that:

(*a*) The deficiency was due to an excessive loss of potassium in the faeces.

(*b*) The degree of this loss of potassium was closely related to the fluid volume of the faeces.

(*c*) The contribution of cellular debris to the potassium loss was of minor importance.

(*d*) Large amounts of potassium chloride given by mouth were required to relieve the symptoms of potassium deficiency.

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A RADIOLOGICAL STUDY OF PULMONARY INFARCTION[1]

By D. S. SHORT

With Plates 22 to 29

The thirteen years since the radiology of pulmonary infarction was last considered in this journal (Smith, 1938) have witnessed an increasing realization of the frequency and importance of thrombo-embolism (Bauer, 1946) especially in patients with heart disease (White, 1940; Carlotti, Hardy, Linton, and White, 1947). At the same time there has been a growth in our knowledge of the use of anticoagulants and other measures in the prevention and treatment of this condition. Notwithstanding these advances, the diagnosis of pulmonary thrombo-embolism is often a matter of considerable difficulty. It is essentially a clinical exercise. Laboratory tests are of little value. A characteristic electrocardiogram is only seen in the small minority of cases which present the picture of acute cor pulmonale. Undoubtedly the greatest help comes from a radiological examination. Smith's (1938) paper, based on 13 cases, classified the radiological appearances under six heads:

1. Hazy horizontal clouding at the base.
2. Shadows suggesting pleural effusion.
3. Shadows of roughly circular form, suggesting lung abscess.
4. Density of one part of a lobe, with cavity formation.
5. Basal collapse of a lobe.
6. Linear shadows.

His review of the literature need not be recapitulated here, though mention should be made of Wharton and Pierson (1922). These authors, who were among the earliest writers on the subject, claimed that radiography sometimes established the presence of lesions which had failed to develop characteristic physical signs. In the year in which Smith's paper appeared, Westermark (1938) reported that in cases of embolism without infarction a wedge-shaped avascular area might be seen corresponding to the distribution of the occluded artery. In the following year Jellen (1939), in a review of 18 cases, emphasized the frequent occurrence of elevation of the diaphragm on the side of the lesion. The most important paper on the subject is that of Hampton and Castleman (1940), who used post-mortem radiography to correlate the radiological picture of pulmonary infarction with autopsy findings. From their study of 56 cases they showed conclusively that a wedge-shaped shadow was not to be expected in the great majority of cases. They also stressed the importance of incomplete infarction, and showed that healing and healed infarcts could be recognized in some cases as linear shadows. They elaborated this theme in greater detail in a

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subsequent paper in conjunction with Fleischner (1941). Hampton and Castleman concluded that the value of radiography was such that a diagnosis of pulmonary infarction might be made with confidence despite an inconclusive clinical history. The advantages of their method of study in providing a technically perfect film, and in enabling the radiographic appearances to be confidently correlated with the autopsy findings, are obvious. The great disadvantage is the alteration in the position of the diaphragm. The post-mortem radiograph shows this structure two spaces higher than in life, and the left dome may be further elevated by gastric distension. In addition there is a reduction in size of the cardiovascular shadows. As a result of these factors their paper minimizes the value of elevation of the diaphragm as a sign of pulmonary infarction, and underestimates the difficulty caused by cardiac enlargement and pulmonary congestion. There have been only two papers of note since 1940. In 1943 Homans drew attention to 11 cases in which pulmonary embolism or infarction occurred in healthy persons as a sequel to silent deep thrombosis in the leg veins. He affirmed that a radiologically clear lung field was consistent with serious and repeated embolism. Two years later Krause (1945) published a paper, based on 73 cases, in which he described in detail the radiological appearances of pulmonary infarction with particular emphasis on the differential diagnosis.

Material

The following study is based on 120 cases of pulmonary thrombo-embolism, 85 of which were examined by the author. One hundred and thirteen were diagnosed in Southmead General Hospital, Bristol, between October 1, 1947, and March 31, 1950, and the remainder were seen elsewhere during the same period. The cases not seen by the author fall into two groups—those which were rapidly fatal, and those in which the diagnosis was not made until after death or discharge from hospital. Autopsy revealed a certain number of unsuspected infarcts, and eight cases were diagnosed in retrospect by looking up the notes of all patients from the surgical and obstetrical wards who had chest radiographs taken after operation or in the puerperium. Besides the 120 definite cases presented here, a further 30 patients were seen in whom the diagnosis of pulmonary infarction seemed probable. They have not been included, either because the evidence was inadequate or because it was impossible to exclude an alternative diagnosis. Table I analyses the cases according to the underlying disease. A little less than half the patients were suffering from heart disease, one-quarter had recently undergone operation, one-sixth were obstetrical, and the remainder formed a large miscellaneous group. Table II shows the proportion in which the different aetiological types of heart disease were represented. Rheumatic heart disease accounted for almost half of the group, hypertensive and coronary disease for just under a quarter each.

Comparison with other pulmonary diseases. Pulmonary thrombo-embolism appears to have been the commonest of all serious acute pulmonary diseases during this period (Table III).

Radiology

Ninety-four of the 120 patients on whom this paper is based were examined radiologically after embolism or infarction. In most instances the first examination had to be conducted at the bedside, and consisted in the exposure of a single

TABLE I

Aetiology

Aetiology	*Number of cases*	*Infarction*	*Embolism without infarction*	*X-ray examination*
Heart-disease . .	54	53	1	44
Post-operative . .	30	22	8	21
Obstetrical . . .	20	19	2*	20
Miscellaneous . .	16	12	5*	9
Total . . .	120	106	16	94

* In two cases pulmonary infarction was followed by fatal embolism.

TABLE II

Aetiological Types of Heart Disease

Type	*Number of cases*	%
Rheumatic . . .	26	45·5
Hypertensive . . .	13	23
Coronary	14	24·5
Miscellaneous . . .	4	7
Total	57	100

Two obstetrical cases with rheumatic heart disease and a post-operative case with coronary heart disease are included.

TABLE III

Hospital Admissions of the Major Pulmonary Diseases (Excluding Tuberculosis) in Two and a Half Years

Disease	*Number of admissions*
Primary pleural effusion . .	33
Primary carcinoma of lung . .	50
Lobar pneumonia . . .	100*
Pulmonary thrombo-embolism .	113

* This figure from the hospital records may include some cases of bronchopneumonia and virus pneumonitis; it is probably too high.

anteroposterior film. Sixty-five had more than one examination, including in some cases a lateral view or radioscopy. An abnormal radiograph was seen in 85 cases. In 75 (88 per cent.) the infarct itself was visualized. Pleurisy and elevation of the diaphragm were noted in over half and in over one-third of the cases respectively. Fig. 1 shows the combinations in which the principal radiological features were met with.

The infarct shadow

Site and number. Approximately half the infarcts were situated in the right lower lobe and one-third in the left lower lobe. Multiple pulmonary infarction was seen radiologically in 43 per cent. of cases; if clinical evidence is added to that of the radiograph, the proportion is raised to 52 per cent.

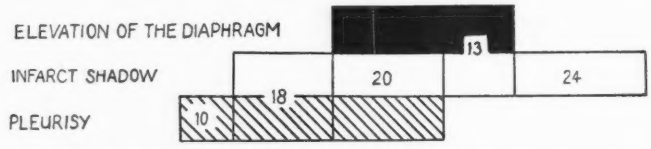

FIG. 1. Principal radiological features and their combinations.

Appearance. Table IV classifies the appearances presented by the infarct shadow. Most frequently they took the form of a more or less well-defined area of consolidation (Plate 22, Fig. 3). This appearance was noted in a high proportion of patients with heart disease, though in the presence of severe pulmonary congestion the lesion was sometimes obscured. There was an important subgroup in which the consolidation occupied the costophrenic angle (Plate 22, Fig. 4), a situation in which it might be mistaken for a small pleural effusion.

TABLE IV

Classification of the Infarct Shadow

Appearance	*Number*
Consolidation	69
Basal clouding	25
Costophrenic shadow	15
Linear shadow	13
Triangular shadow	4
Scar	2
Collapse	1

Seven infarcts appear under more than one heading, e.g. consolidation and linear shadow. The one case of lung abscess in this series was not examined until after the abscess had ruptured into the pleural cavity.

A triangular shadow was observed in only four cases. In approximately one-fifth of the cases the infarcted area was represented by hazy clouding or streaking at one base (Plate 23, Fig. 5). This appearance was seldom seen in patients with heart disease, but it was not uncommon in post-operative and obstetrical cases. In some instances basal clouding, seen in a radiograph taken within a few hours of infarction, changed into well-defined consolidation four to seven days later. Linear shadows (Plate 25, Figs. 9, 10, 11) were only seen in uncongested lungs. No absolute significance attaches to the above classification of shadows, for the proportion of cases in the various categories is dependent upon several variable factors, such as the interval between infarction and radiographic examination and the proportion of patients with pulmonary congestion. The lack of density of an infarct shadow is a frequent source of disappointment. As a rule the lesion is considerably smaller than that of lobar pneumonia, so that

its shadow is correspondingly less dense. In several instances autopsy revealed infarcts which had not been demonstrated by radiography, though they were undoubtedly present when the radiograph was taken (Plate 23, Fig. 6).

Radiographic examination shortly after infarction. It is well recognized that a shadow may not appear on the radiograph for several hours after pulmonary infarction (Farr and Spiegel, 1929). Seven cases in the present series were examined within 12 hours of infarction; three showed a well-defined consolidation, one basal clouding, and three no shadow. Eight cases were examined between 12 and 60 hours after infarction; a well-defined shadow was present in five, and basal clouding in the remaining three. It appears therefore that a shadow is often absent within 12 hours of infarction, but after that time it can usually be seen.

Rate of resolution. Most estimates of the rate of resolution of pulmonary infarcts are based on post-operative cases, and emphasize the rapidity of the process. Hampton and Castleman (1940) reported a shadow clearing in two to four days; Cutler and Hunt (1922) stated that the radiograph returned to normal within a week, and Kerley (1936) noted that infarcts vanished, or became greatly reduced in size, in a fortnight. Resolution may, however, be much more protracted, particularly in patients with heart disease; Scherf and Boyd (1948) mentioned that the shadow might persist as long as two or three months. In the present series there were 30 cases in which a clear history of onset, and the slightness of pleural reaction, enabled the rate of resolution to be determined. Ten were patients with heart disease, and 20 (one of them with two infarcts) had a normal cardiovascular system. In the latter group (Table V) about half the

TABLE V

Rate of Resolution in the Presence or Absence of Heart Disease

	Number of infarcts	*Number resolved in*				
		2 weeks	*4 weeks*	*6 weeks*	*8 weeks*	*10 weeks*
With heart disease .	10	2 (20%)	5 (50%)	6 (60%)	9 (90%)	10 (100%)
Without heart disease .	21	10 (48%)	18 (86%)	19 (90%)	21 (100%)	
Total . .	31	12 (39%)	23 (74%)	25 (81%)	30 (97%)	31 (100%)

infarcts resolved within a fortnight, and less than one-sixth persisted beyond four weeks. Three infarcts were seen to resolve in two to five, five, and seven days respectively. In patients with heart disease only one-fifth resolved in under a fortnight, and almost half persisted for a month or more. Nearly all these patients had considerable pulmonary congestion, and this must be regarded as the chief cause of the delay in resolution. There was also evidence that small infarcts resolve more rapidly than large ones, but this observation was complicated by the fact that an undue proportion of large infarcts were found in cases with considerable pulmonary congestion.

Scars. Of the 30 cases followed by serial radiography, a definite scar was visible in the follow-up in only one, a patient with congestive heart failure. It

had the appearance of a network of fine lines (Plate 24, Fig. 7). Another form of scarring was seen in a patient (not in the present series) who attended the hospital for chest radiography during the period under review. She had undergone appendicectomy a year previously, and her convalescence had been complicated by massive pulmonary infarction. The radiograph (Plate 24, Fig. 8) showed a scar resembling a knot with radiating strands. This patient showed no evidence of heart disease, and at no time did the radiograph suggest pulmonary congestion.

Linear shadows. Transient linear shadows were commonly observed during the process of resolution. They were of three types. (1) *Pleural.* Thickening of the horizontal fissure is a common accompaniment of infarction of the middle or upper lobes of the right lung. Less common is thickening of the inconstant pleural fold which separates the cardiac segment from the remainder of the right lower lobe. This was observed in several cases in which the lower lobe was infarcted, as a line rising from the mid-point of the diaphragm and curving upwards and medially for about 1½ inches (Plate 22, Fig. 4). (2) *Linear atelectasis.* In six cases one or two well-defined lines were seen running horizontally, sometimes with a little undulation, across the lower zone (Plate 25, Fig. 9). In two cases the lines were shorter, and situated in the costophrenic and cardiophrenic angles respectively. In three cases there was well-marked elevation of the diaphragm on the affected side; in the remaining five this could not be determined owing to involvement of the opposite base by a second infarct. In each case pulmonary congestion was absent or slight. Five were followed to complete clearance, a process which took less than a fortnight in three cases, three weeks in one, and a month in the last. Linear atelectasis is not infrequently encountered in chest radiography, but the underlying pathology is uncertain, since cases rarely come to autopsy. Although Shanks, Kerley, and Twining (1938) did not include pulmonary infarction in their list of aetiological factors, the only histological examination which they quoted is very suggestive of it. (3) *Dense bands or plates.* This striking feature, which was observed in four cases, consisted of one thick horizontal or oblique line in a postero-anterior radiograph, two to three inches long and not extending completely across the lobe (Plate 25, Figs. 10, 11). Radioscopy showed it to lie within the lung parenchyma. As with linear atelectasis, elevation of the diaphragm and absence of notable pulmonary congestion were prominent features. These shadows generally appeared later and persisted longer than the thin lines. In three cases the dense band did not appear for three weeks (in one case not for 10 weeks), and took five to ten weeks to resolve. In the fourth it was present in the first film taken, three days after infarction, and disappeared in three weeks.

Smith (1938) suggested that linear shadows might in some cases represent the opacity of a blood-vessel which had undergone thrombosis. Accepting Lodge's (1946) description of the radiographic anatomy of the pulmonary arteries and veins, it was found that none of the linear shadows observed in the present series corresponded to the position of any of the pulmonary blood-vessels. It seems likely that both the thin and the thick linear shadows are

atelectatic. The frequently associated elevation of the diaphragm supports this view, and the fact that the linear shadows were not observed in the presence of severe or moderate pulmonary congestion is doubtless due to the difficulty with which congested lung collapses.

Two uncommon appearances must be mentioned: (1) *Lung abscess.* An abscess may result either from an infected embolus or from secondary infection of a bland infarct. The only such case in the present series was an example of the latter aetiology. Lung abscess and ring shadows have figured prominently in previous accounts of the radiology of pulmonary infarction (Smith, 1938; Sante, 1945), but now they are uncommon. The decline is probably attributable to the widespread employment of efficient chemotherapy. (2) *Localized avascularity.* There was one doubtful example of the embolic translucency described by Westermark (1938), in a radiograph which showed evidence of two definite pulmonary infarcts.

Pleurisy

Radiological evidence of pleural involvement was found in 48 cases (Table VI), or 56 per cent. of those showing positive evidence of pulmonary infarction. An

TABLE VI

The Incidence of Pleurisy

	Number of cases	*Pleurisy*	*Effusion*
With heart disease . .	44	18 (41%)	14 (32%)
Without heart disease . .	50	30 (60%)	14 (28%)
Total	94	48 (51%)	28 (30%)

effusion was seen in 28 cases (33 per cent.), varying in size from the smallest collection in the costophrenic angle to an amount sufficient to obscure three-quarters of the hemithorax. In the absence of heart disease effusions were never large, and probably never exceeded half a litre. The fluid was examined in 17 cases, either by aspiration or at autopsy, and was found to be haemorrhagic in eight. Pleural thickening or adhesion was noted in 20 cases apart from effusion, manifesting itself frequently as a tenting of the diaphragm. In 12 other cases similar appearances were seen after the absorption of an effusion. Hydrothorax was seen radiologically in 48 per cent. of the cases with heart disease. In 32 per cent. it could be regarded as the sequel of infarction, and in these cases the fluid was frequently observed to persist for weeks or months, despite an otherwise satisfactory response to treatment.

Elevation of the diaphragm

Elevation of the diaphragm on the side of the lesion, with restriction of its excursion, was a striking feature in 35 per cent. of the 94 cases examined[2] and

[2] Elevation was regarded as being present if any of the following criteria were satisfied: 1. Right dome at least 1½ inches higher than the left. 2. Left dome higher than the right. 3. Either dome unequivocally raised by comparison with a radiograph taken under identical conditions either before the appearance of the infarct or after resolution.

thus forms, with the infarct shadow and pleurisy, the triad in the radiological diagnosis of pulmonary infarction. It was more frequently observed in the absence of pulmonary congestion, being found in 50 per cent. of the cases without heart disease. In several instances it was so marked as to lead to a suspicion of lower lobe collapse (Plate 26, Fig. 12); sometimes it entirely obscured an infarct in the posterior basal segment of the lower lobe (Plate 27, Fig. 13), and in three cases extreme elevation of the right dome, associated with lateral adhesion of the pleura, led to a diagnosis of pleural effusion and an attempted aspiration (Plate 28, Fig. 14). Elevation of the diaphragm was always associated with a lesion in the corresponding lower lobe. Of the 31 cases exhibiting this sign 17 had infarcts in the right lower lobe, 11 in the left lower lobe, and in two cases there was bilateral elevation of the diaphragm with infarcts at both bases. In one case with convincing clinical evidence of infarction the right dome was raised without any other radiological evidence of infarction (Plate 29, Fig. 15). The position of the diaphragm usually returned to normal as the infarct resolved, though in one case elevation persisted for a fortnight after apparently complete resolution.

The negative radiograph

In nine cases with undoubted thrombo-embolic disease of the lung the radiograph was normal. One or more of the following factors may have been responsible: (1) *Infarct shadow hidden behind diaphragm or heart.* About 80 per cent. of pulmonary infarcts occur in the lower lobes, and some are concealed either by elevation of the diaphragm or, in patients with heart disease, by cardiac enlargement. (2) *Pulmonary congestion.* As noted by Rieder and Rosenthal (1925), severe pulmonary congestion may render an infarct invisible. (3) *Hydrothorax.* A pleural effusion resulting from cardiac failure or renal disease may hide an infarct in the underlying lung. It is the combination of factors 1, 2, and 3 that makes the diagnosis of pulmonary infarction in heart disease particularly difficult. (4) *Embolism without infarction.* This undoubtedly occurs (Homans, 1943) and in such cases Westermark's sign should be carefully sought for. (5) *Examination made too soon or too late.* In some cases a shadow does not appear for 12 hours, and in an uncongested lung resolution may take place within a week. In either case elevation of the diaphragm may provide a clue, and after resolution pleurisy may remain. (6) *Inadequate technique.* It is probable that in at least one case radiographic confirmation was not obtained owing to a mistake in the exposure.

When a negative radiograph is obtained in a patient suspected of pulmonary embolism or infarction, confirmation of the diagnosis should be sought in the following ways: (1) *Re-examination.* The importance of repeated examinations in this condition cannot be over-emphasized. (2) *Lateral radiograph.* This may reveal an infarct behind the diaphragm or heart. (3) *Radioscopy.* By this means a shadow may be visualized which was hidden in the radiographs, and its shape determined. The diaphragmatic excursion can also be observed. (4) *Tomography.* This technique sometimes succeeds in demonstrating an infarct

which, in the ordinary radiograph, is completely obscured by pleural effusion (Gaskell, 1950).

Discussion

The radiological picture

If the clinical features of pulmonary infarction are typical, little or nothing is demanded of the radiological examination. Where the history is atypical or is lacking, a characteristic radiographic picture may supply a diagnosis that would not otherwise have been considered. Since the illusion popularized by Wessler and Jaches (1923) is still being perpetuated (Sante, 1945), it is necessary to emphasize that a triangular shadow with its apex toward the heart is not to be expected. It was found in only 5 per cent. of the present series. In the majority of cases the shape of the shadow in the postero-anterior radiograph is not characteristic. Hampton and Castleman (1940) dissected out 10 pulmonary infarcts from one patient at autopsy, and demonstrated that the majority were quite irregular in shape. They further showed that even when an infarct was pyramidal a triangular appearance was not often seen in the radiograph, since the surroundings of the infarct were often radio-opaque. In the costophrenic sulcus, for instance, an infarct appears merely as an opacity filling the angle between the chest wall and the diaphragm. Moreover, a pyramidal lesion only casts a triangular shadow within a narrow range of projections. In most situations the axis of the infarct is at some other angle than 90° to the postero-anterior projection, so that its shadow is distorted. Yet another reason for an irregular opacity is the superimposition of two infarct shadows. From the foregoing it should be clear that a triangular shadow will only be seen in the radiograph if four criteria are satisfied. The infarct itself must be pyramidal, its sides must be bordered by translucent tissues, its axis must lie at a right angle to the X-rays, and it must not be overlapped by another infarct.

Diagnosis

Errors in the radiological diagnosis of pulmonary infarction usually occur because the condition is not suspected; but even when an infarct is suspected, differentiation from such conditions as collapse, subphrenic abscess, lobar pneumonia, and pleural effusion may be exceedingly difficult.

Collapse. The radiological appearances of pulmonary infarction may at different times suggest either massive or minimal collapse.

1. *Massive collapse* may be closely simulated if marked elevation of the diaphragm is accompanied by shrinkage of the lower lobe. Collapse and infarction are both well recognized post-operative complications. In attempting a differentiation four points should be borne in mind: (1) Eighty per cent. of cases of massive collapse occur within the first 48 hours (Scott, 1925), whereas infarction is common throughout the first three weeks, after operation. (2) Cardiac displacement is a striking feature in massive collapse, but is usually absent in thrombo-embolic disease. (3) Evidence of pleurisy is rare in massive collapse,

whereas it is common in pulmonary infarction. (4) Re-examination after a few days may confirm the diagnosis of infarction by showing a well-defined area of consolidation (Plate 26, Fig. 12).

2. *Post-operative pulmonary hypoventilation.* Muller, Overholt, and Pendergrass (1929), and more recently Howkins (1948), have demonstrated that after operation one or both domes of the diaphragm may be elevated and show diminished excursion. These authors also noted atelectatic changes in the lung parenchyma and an increase in the normal markings, particularly in the lower lobes. Unlike the picture of pulmonary infarction, there is no discrete infarct shadow, the signs are maximal immediately after operation (probably clearing in most cases within a week), and there is no pleural involvement. Clinically the condition is symptomless and afebrile.

3. *Linear atelectasis.* It has been pointed out above that an embolic lesion should be considered in the differential diagnosis of linear atelectasis. Other suggestive signs may be present, such as recent pleural involvement related to the affected lobe, or evidence of infarction in another lobe.

Subphrenic abscess. When radioscopic examination of a patient who has recently undergone abdominal operation reveals a raised, immobile dome with overlying pleural reaction, the differentiation between subphrenic abscess and pulmonary infarction may be exceedingly difficult. Even the presence of a shadow in the lung parenchyma overlying the dome is not conclusive evidence of pulmonary infarction (Overholt and Donchess, 1935; Neuhof and Schlossmann, 1942; Harley, 1949). The history and physical examination may suggest the correct diagnosis. A difficult operation with soiling of the peritoneum makes subphrenic abscess a possibility. Moreover in this condition fever is usually present from the day of operation, whereas in thrombo-embolic disease the rise of temperature occurs at the onset of infarction, most commonly during the second week after operation. The presence of an abscess may be suggested by evidence of localized peritonitis on abdominal examination, or by tenderness on percussion over the lower ribs. Radiologically the crucial points are the character of the shadow, if any, in the lung parenchyma, and the appearance of the diaphragm. In subphrenic abscess, when a lesion is present in the overlying lung, it is mottled and resembles bronchopneumonia; later it may show a cavity. An infarct never has this appearance in the absence of secondary infection. The diaphragm in subphrenic abscess is described as being blurred and thickened; this is not so in pulmonary infarction.

Lobar pneumonia. The differentiation between lobar pneumonia and pulmonary infarction may present difficulty. A rigor or chill, the presence of herpes labialis, and a striking response to specific chemotherapy suggest lobar pneumonia; the finding of heart disease, auricular fibrillation, venous thrombosis, or a history of recent operation or confinement suggest pulmonary infarction. When none of these clues are present the radiological examination may be of the utmost importance. Lobar pneumonia frequently involves the entire lobe, whereas an infarct is usually much smaller, and for this reason its shadow is also less dense. In pneumonia the shadow is sometimes seen to increase rapidly

in size for 24 to 48 hours, even though the patient is responding favourably to chemotherapy. This picture is not seen in infarction. Though some elevation of the diaphragm is common in lobar pneumonia (Wu, 1932), it is more frequent and more marked in pulmonary infarction.

Pleural effusion. A small effusion may have to be differentiated from a pulmonary infarct, and a larger effusion may raise the question of underlying

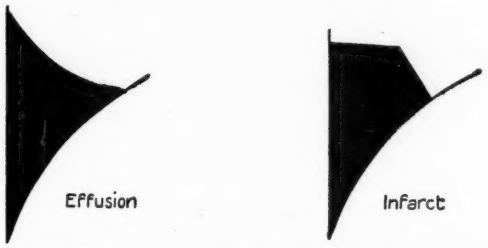

FIG. 2. The appearance of an infarct in the costophrenic angle contrasted with a small effusion (diagrammatic).

infarction. (1) *Costophrenic infarct.* An infarct in the costophrenic angle may resemble a small collection of fluid. Differentiation is based on the appearance of the upper border of the shadow. In the case of fluid it is concave upward and higher laterally; in the case of an infarct it is more often irregular or humped, that is, convex upward (Fig. 2). Radioscopy should enable the diagnosis to be confirmed. (2) *Infarct underlying pleural effusion.* In a patient with pleural effusion an underlying pulmonary infarction may be suggested by a history of recent operation or childbirth, or by the presence of cardiac enlargement. In a patient with heart disease a unilateral hydrothorax, persisting for months despite an otherwise satisfactory response to treatment, suggests underlying lung disease, usually an infarct. The lesion may sometimes be demonstrated by tomography.

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Summary

Pulmonary thrombo-embolism was diagnosed during a period of 30 months in 120 patients, of whom 113 were in the wards of a general hospital. The incidence of pulmonary thrombo-embolism in this hospital was higher than that of lobar pneumonia.

Of 94 patients examined radiologically 85 showed some abnormality indicative of infarction—an infarct shadow in 88 per cent., pleurisy in 56 per cent., and elevation of the diaphragm in 39 per cent.

The various types of infarct shadow are described, and also the linear shadows and bands which may be seen in the process of resolution.

No ring shadow was seen, and there was only one case of lung abscess in the series. Both appear to have become uncommon since the sulphonamides and penicillin came into general use.

Seven patients were examined radiographically within 12 hours of infarction. At that stage no shadow was visible in three cases, in one there was basal clouding only, and in the remaining three there was a well-defined opacity.

The interval between infarction and complete resolution could be determined with reasonable accuracy in 31 instances. Fifty per cent. of infarcts in patients with normal hearts cleared within a fortnight, and 83 per cent. within a month. Only 20 per cent. of those in patients with heart disease resolved in a fortnight, and 50 per cent. in a month.

Elevation of the diaphragm was noted in 50 per cent. of the cases without pulmonary congestion. In some it was so marked as to suggest lower lobe collapse, and in several it partially or entirely concealed basal infarcts.

The problem of the negative radiograph is discussed, and suggestions are made regarding the confirmation of the diagnosis in such cases.

Finally some of the more important problems of differential diagnosis are considered.

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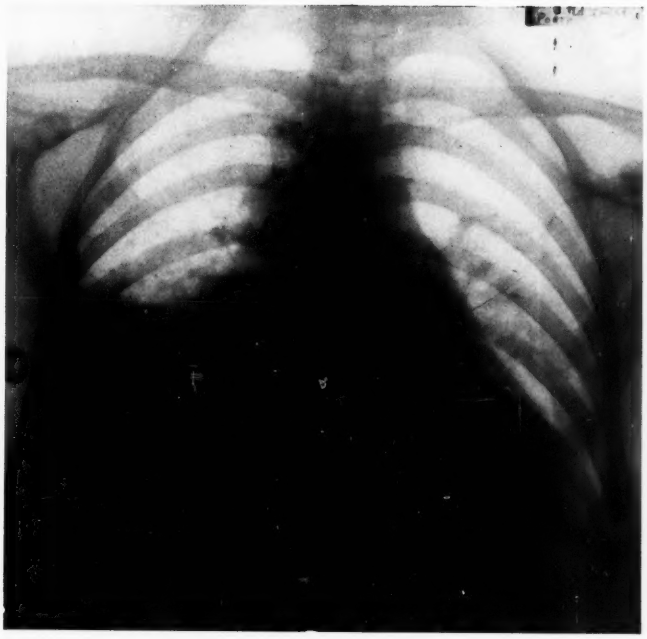


FIG. 3. Infarction of the right middle and lower lobes in a case of mitral stenosis. Autopsy confirmed the diagnosis

FIG. 4. Costophrenic shadow (right) in a case of hypertensive heart disease with pulmonary oedema and multiple pulmonary infarcts. Autopsy confirmed the diagnosis. Note also the linear shadows (pleural) in the right lower zone

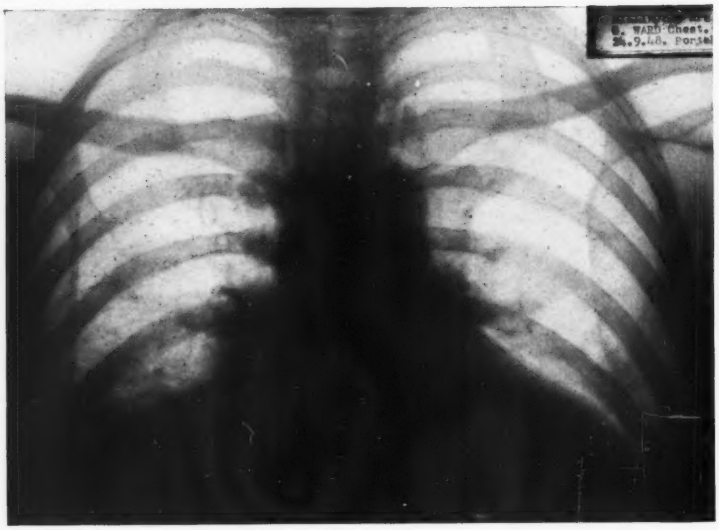


FIG. 5. Basal clouding (right lower zone) in a case of pulmonary embolism secondary to femoral thrombophlebitis

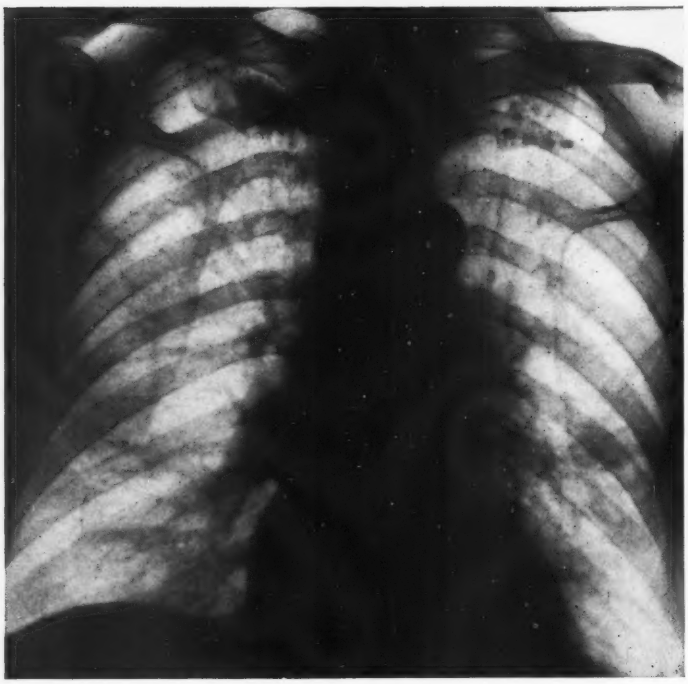


FIG. 6. Infarcts giving rise to inconspicuous shadows. This patient gave a history of cough, haemoptysis, and right-sided pleuritic pain. Examination revealed signs of a large area of consolidation at the right base and râles at the left base. At autopsy, four days after the radiograph was taken, two infarcts were found, one involving half the right lower lobe, and another large one in the lateral part of the left lower lobe. (There was also healed apical tuberculosis)

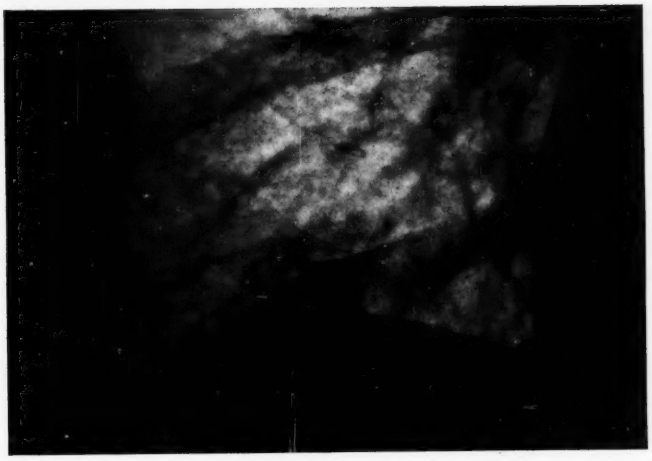


FIG. 7. Linear scars in the right lower zone seven months after infarction in a patient with hypertensive heart disease, thyrotoxicosis, and paroxysmal auricular fibrillation

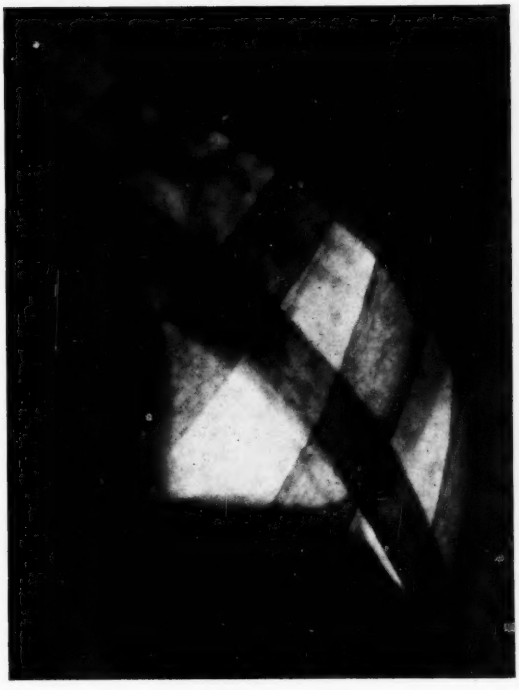


FIG. 8. Nodular scar in the left lower zone two years after infarction following appendicectomy. There was no evidence of heart disease or pulmonary congestion

(By courtesy of Dr. J. V. Sparks)

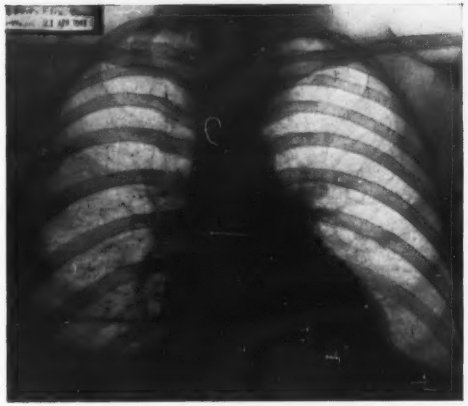


FIG. 9. Linear shadows at the right base 17 days after infarction. 13 days later the radiograph was clear. Bilateral basal infarction followed splenectomy for chronic haemolytic anaemia

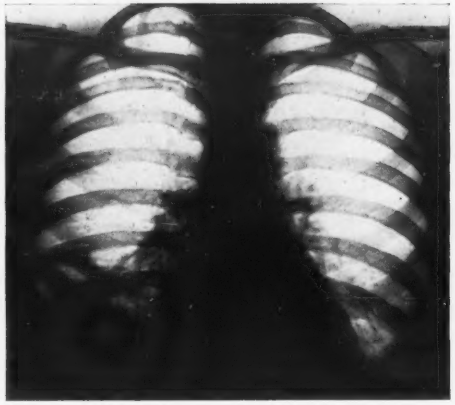


FIG. 10. Dense band, shown by radioscopy to be situated in the right lower lobe, five weeks after infarction. Note elevation of the right dome. Seven days later the shadow was fading

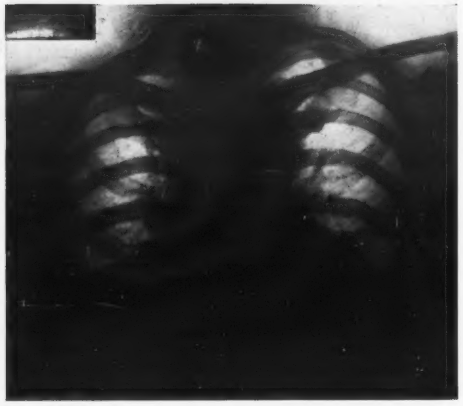
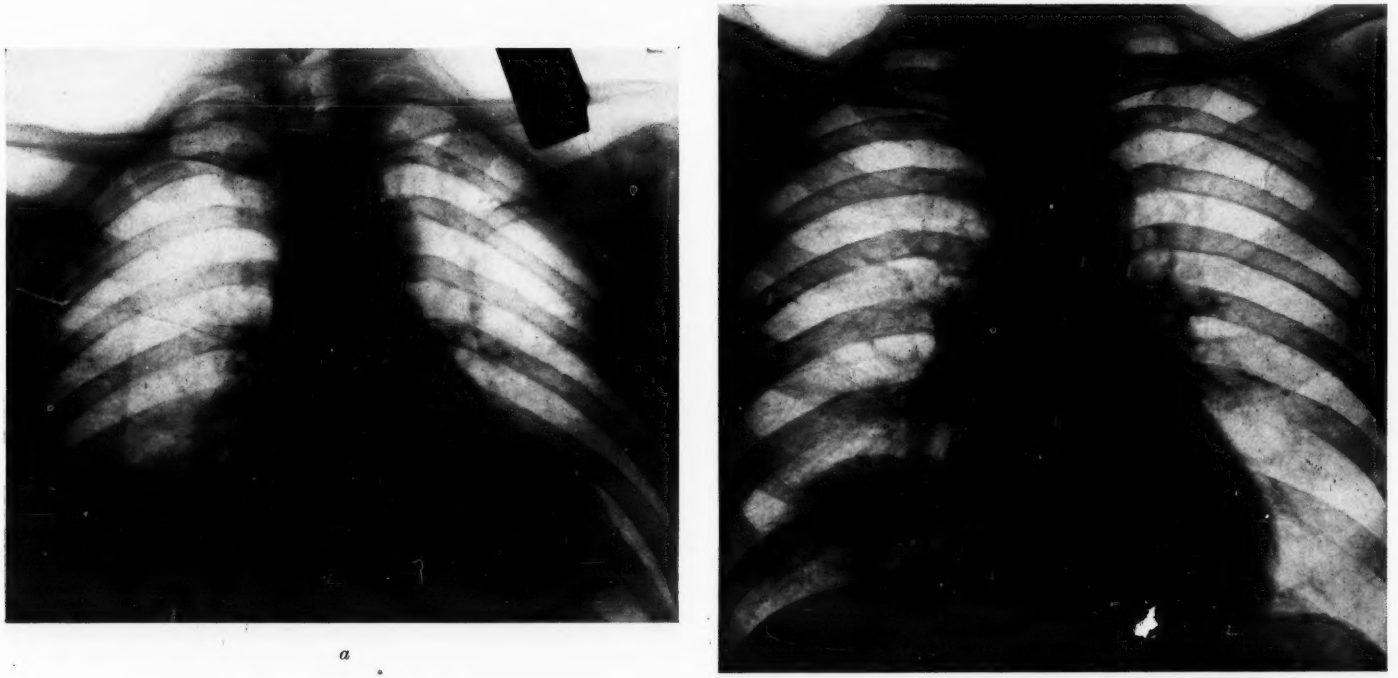
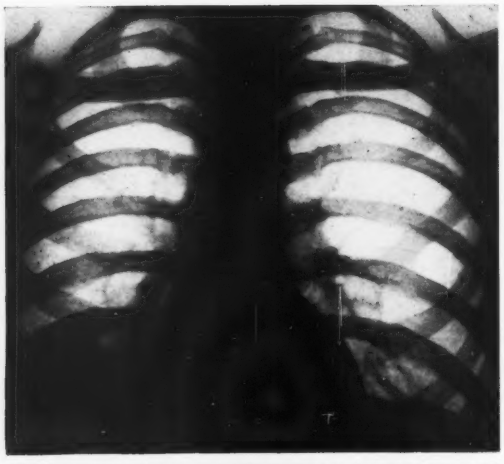


FIG. 11. Dense band, shown by radioscopy to be situated posteriorly in the right lower lobe, three months after infarction. Both domes, though raised, moved well with respiration. Nine weeks later the appearances were essentially unchanged, suggesting organization



a *b*

FIG. 12. Infarction simulating collapse
(*a*) Radiologist reported right lower lobe collapse
(*b*) Re-examination five days later revealed the infarct shadow



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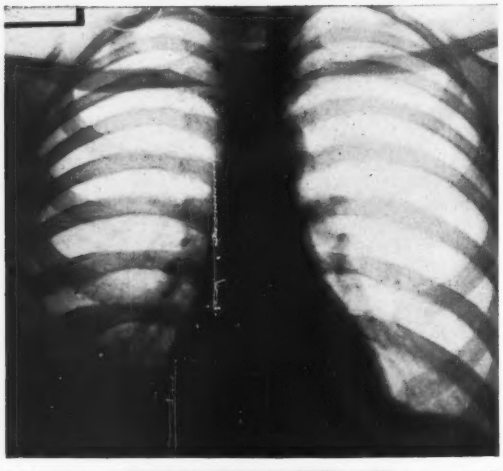

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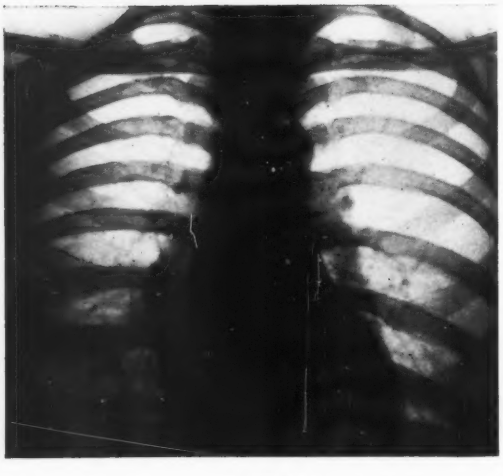

c

FIG. 13

(For description see opposite page)

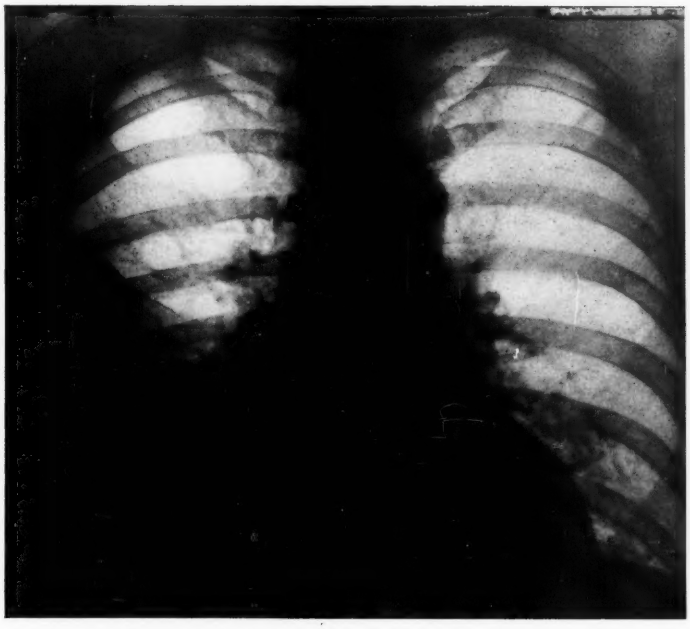

FIG. 14. Right lower lobe infarction with elevation of the diaphragm simulating pleural effusion. Radioscopy showed the right dome greatly raised and peaked laterally. The radiograph was taken 12 days after infarction

PLATE 27, FIG. 13. Infarct concealed by elevation of the diaphragm; pulmonary infarction secondary to puerperal femoral thrombosis.

(*a*) A fortnight after typical symptoms and signs of infarction at both bases. Diaphragm high; no definite shadow.

(*b*) A week later. The right dome has fallen, revealing the infarct.

(*c*) Seven weeks from onset. Diaphragm in normal position.

(All radiographs taken in full inspiration with the patient erect)

a *b* *c*

FIG. 15. Elevation of the diaphragm without other radiographic evidence of pulmonary infarction

(*a*) November 4. Pre-operative radiograph. Four weeks later the patient underwent partial gastrectomy, which was followed by femoral phlebothrombosis and recurrent pulmonary infarction.
(*b*) December 31. Radiograph taken within 12 hours of right basal infarction. Note elevation of the right dome.
(*c*) January 12. After further infarction. Note shadow in the right mid-zone.

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THE CORRELATION BETWEEN THE RADIOLOGICAL APPEARANCES AND THE CLINICAL AND SPIROMETRIC STATE IN EMPHYSEMA[1]

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The radiological appearances of the chest in emphysema are well known, and have been fully described by Kerley (1936) and, as far as the heart is concerned, by Parkinson (1936), Rubin (1936), and Parkinson and Hoyle (1937). Christie (1944*b*) briefly recorded the lack of correlation in his experience between the radiological appearances and the clinical and post-mortem findings, and Parkinson and Hoyle (1937) found that radiology provided additional support of the diagnosis in only half of 80 cases of gross clinical emphysema; but in an extensive search of the literature we have been unable to obtain any precise information regarding the extent to which ventilatory insufficiency can be judged by radiological appearances. The purpose of the present investigation was therefore to ascertain the correlation between the radiological and clinical states of the victims of emphysema.

Scope and Method of the Investigation

Fifty-two cases of varying degrees of emphysema were assessed. The diagnosis was made in the first instance on clinical grounds alone; all the patients complained of cough and dyspnoea either at rest or on exertion, and their diminished exercise tolerance was in no case explicable by primary cardiovascular or blood disease, or by obesity, though three had pulmonary heart failure. The entire group presented some or all of the classical physical signs of emphysema. Early in the investigation it was appreciated that it was in some cases difficult to assess the part played by psychological factors, and it was apparent that clinical assessment alone was sometimes insufficient to give precise quantitative knowledge of the degree of ventilatory insufficiency. Meakins and Christie (1929–30), Hurtado and Boller (1933), Hurtado, Fray, and McCann (1933), Hurtado, Kaltreider, Fray, Brooks, and McCann (1934), Kaltreider, Fray, and Hyde (1938), Aslett, Hart, and McMichael (1939), Christie (1944*a*), and Baldwin, Cournand, and Richards (1949) have all pointed

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out that in emphysema the vital capacity is reduced, and that both the residual air and the ratio of residual air to total lung-volume are increased. The total lung-volume and all its subdivisions were therefore determined in every possible case; but some patients were too ill for this to be carried out, and in one or two instances either the patients' apprehension or their toothless state made it impossible. The vital capacity, complemental air, and reserve air were measured in the usual way on a Benedict-Knipping spirometer, and the functional residual air (and from it the residual air) was determined by the closed circuit constant-volume hydrogen dilution method described by McMichael (1939). During the course of the research hydrogen was replaced by helium to remove any risk of combustion. Recalibration of the apparatus was necessary, but the change did not introduce any systematic error. Radiographs were taken postero-anteriorly and laterally, in the erect posture at full inspiration, at a distance of six feet. In addition almost all subjects were screened by two observers.

In order to preserve simplicity of deduction the subjects were divided on clinical grounds into only two main groups: those dyspnoeic at rest, and those not dyspnoeic at rest but unduly so on exertion. The former were regarded as severely and the latter as moderately emphysematous. From Tables II and III, which summarize the spirometric findings, it will be seen that this clinical assessment of the degree of emphysema was fully confirmed spirometrically. It must be added that dyspnoea resulting from bronchospasm was disregarded, and subjects were grouped according to their ventilatory status when no actual asthma was present. It is, of course, obvious that radiological appearances are influenced by the factors that have played a part in the production of the emphysematous change. In particular we suspected that the radiological appearances in emphysema resulting from asthma might differ from those in emphysema due to chronic bronchitis. We therefore further divided our subjects into those whose emphysema resulted from asthma and those in whom it was due to other causes. This subdivision into four groups according to aetiology and severity is summarized in Table I. It is realized that such an aetiological classification is superficial, in that it takes no account of the predisposing factors, for example in the elastic tissue, which determine the resistance of the individual's lungs to the development of emphysema. It will be seen that the groups in which emphysema was due to asthma comprise chiefly women, and that their mean age is much lower than that of the patients with emphysema due to other causes, about 93 per cent. of whom were men. Other partial aetiological factors, which for the sake of simplicity are not shown in Table I, were poison gas in the first world war (four cases: three severe, of which one is listed under asthma, one under chronic bronchitis, and one under silicosis; and one moderate case shown as due to chronic bronchitis), and bronchiectasis (at least two cases, one severe and one moderate, both listed under chronic bronchitis). In three other cases listed under chronic bronchitis the absence of sputum suggested that a 'primary' degeneration of elastic tissue in the lungs may possibly have been the main aetiological factor.

TABLE I

Distribution of Cases according to Aetiology and Severity of Emphysema

Degree of emphysema	*Aetiological factors*	*Number of subjects*			*Age in years*	
		Total	*Male*	*Female*	*Mean*	*Range*
Severe	Asthma	3	2	1	44·7	29–64
	Other causes:					
	Chronic bronchitis	11	11	..	52·6	41–63
	Silicosis	5	5	..	53·6	48–57
	Inhalation of sulphur dioxide	1	1	..	60·0	..
Moderate	Asthma	8	0	8	31·8	15–47
	Chronic bronchitis	24	21	3	51·5	35–69

Results

A. *Spirometric findings*

In a previous communication some of us (Whitfield, Waterhouse, and Arnott, 1950) published the results of our determinations of the total lung-volume and its subdivisions in 64 normal male and 32 normal female subjects. The mean absolute values obtained are quoted in Table II, which also shows the means of the absolute results of lung-volume measurements in the various groups of emphysematous subjects included in the present investigation. It

TABLE II

Spirometric Findings Compared with Normal Subjects (Mean Absolute Values in Litres)

Division of Lung-volume	*Men*			*Women*			
	Normal (64)	*Moderate emphysema, non-asthmatic (18)*	*Severe emphysema, non-asthmatic (14)*	*Normal (32)*	*Moderate emphysema, non-asthmatic (3)*	*Moderate emphysema, asthmatic (8)*	*Severe emphysema, asthmatic (1)*
Total lung-volume	5·74	6·17	5·74	4·28	4·67	4·95	4·35
Vital capacity .	4·00	3·31	2·22	2·87	2·00	2·51	1·54
Complemental air .	2·73	2·26	1·52	1·99	1·45	1·71	0·85
Reserve air . .	1·27	1·05	0·70	0·88	0·53	0·80	0·69
Functional residual air	3·02	3·91	4·21	2·29	3·20	3·24	3·50
Residual air .	1·75	2·86	3·51	1·41	2·67	2·44	2·81

will be noticed that the total lung-volume is greater in the moderately emphysematous than in normal subjects, while in the severely emphysematous it is near the normal. The vital capacity and its two components, the complemental and reserve air, are all reduced in the emphysematous subjects, and the reduction is considerably greater in the severe than in the moderate group. The functional residual air and residual air are both greatly increased in the patients with emphysema, and this increase also is much more marked in the severely emphysematous than in the moderate cases. It has become current

practice to speak of the various divisions of lung-volume as percentages of the total lung-volume, and in particular the ratio of residual air to total lung-volume is recognized as a valuable index of ventilatory efficiency (Meakins and Christie, 1929–30; Hurtado and Boller, 1933; Hurtado, Kaltreider, Fray, Brooks, and McCann, 1934; Kaltreider, Fray, and Hyde, 1938; Aslett, Hart, and McMichael, 1939). The mean results of our previously published determinations of the percentage values of the various divisions of lung-volume in normal subjects (Whitfield, Waterhouse, and Arnott, 1950) are quoted in Table III,

TABLE III

Spirometric Findings Compared with Normal Subjects (Mean Percentage Values)

	Men			*Women*			
Division of Lung-volume	*Normal (64)*	*Moderate emphysema, non-asthmatic (18)*	*Severe emphysema, non-asthmatic (14)*	*Normal (32)*	*Moderate emphysema, non-asthmatic (3)*	*Moderate emphysema, asthmatic (8)*	*Severe emphysema, asthmatic (1)*
Vital capacity / Total lung-volume	69·8	53·9	38·5	67·8	43·7	50·5	36·0
Complemental air / Total lung-volume	47·8	36·6	26·3	47·4	31·7	34·2	20·0
Reserve air / Total lung-volume	22·0	17·3	12·2	20·4	12·0	16·3	16·0
Functional residual air / Total lung-volume	52·2	63·4	73·7	52·6	68·3	65·8	80·0
Residual air / Total lung-volume	30·2	46·1	61·5	32·2	56·3	49·5	64·0

which also shows the mean percentage values for the emphysematous subjects included in this study. The reduction of the vital capacity, complemental air and reserve air, and the increase of the functional residual air and residual air, in the emphysematous are again seen to be marked, and these changes are much greater in the severe than in the moderate group. Our clinical grouping of the cases of emphysema is therefore fully justified on spirometric grounds.

B. *Radiological findings*

1. *Increased lung translucency.* Over-translucency of the lung fields is probably the best-known radiological sign of emphysema. While there is no doubt of its value as evidence of emphysematous change, there are many factors affecting its reliability. First, its presence and degree is a visual impression difficult of precise quantitative measurement; secondly, in an over-penetrated film normal lungs appear over-translucent, while in a 'soft' film emphysematous lungs appear to have a normal translucency; thirdly, the presence of an element of fibrosis, whether of silicotic or other origin, or of bronchiectasis, diminishes

translucency; and fourthly, when polycythaemia and congestive cardiac failure supervene the congestion of the lung fields masks the abnormal translucency, and it may only be evident at the lung bases. We assessed the translucency of the lung fields in all our cases. There is no doubt that over-translucency is frequently more evident at the bases than in the upper zones. This may be partly due to the shadow of the pectoralis major muscle diminishing translucency in the upper part of the chest, but it is difficult to believe that this factor is solely responsible. In half of the cases we studied the bases were more translucent than the remainder of the lung fields, but this phenomenon showed no relationship to the severity or aetiology of the emphysematous process. The general translucency of the lung fields in postero-anterior films was increased in all patients of the asthmatic group, and in all but 10 of those whose emphysema was due to other causes. Of these 10 cases seven were classified as severe, and three as moderate. Of the seven severe cases the lack of translucency was explicable in six, by silicosis (two cases), polycythaemia (one case), congestive cardiac failure (two cases), and bronchiectasis (one case), but in the remaining case and in the three moderate cases no reason for the lack of translucency was apparent. In only four (one silicotic, one with congestive cardiac failure) of these 10 cases was increased basal translucency not evident. Over-translucency and increase in the area of the retrocardiac window in lateral films proved to be a more constant feature than generalized over-translucency in posterio-anterior films. The retrocardiac window was abnormally translucent in all but two patients of the whole series: one was a mild case, and the other had congestive cardiac failure. In addition, all but 10 cases showed an abnormally translucent anterocardiac window. Of these 10 two were moderate cases due to asthma, four were mild cases due to other causes, and three were severe cases—two silicotic, and one with congestive cardiac failure. Over-translucency can therefore be regarded as a moderately reliable radiological sign of emphysema, but for a variety of reasons, known and unknown, emphysema of severe degree may be present without obviously increased translucency. Marked over-translucency is suggestive of an asthmatic origin, and consideration of the retrocardiac window and of the comparative translucency of the lung bases appears more important than assessment of the appearance of the lung fields as a whole.

2. *The heart.* In a postero-anterior radiograph the heart in emphysematous subjects often appears small, and often ptotic. According to Kerley (1936) and Parkinson (1936) the explanation of this appearance is first that, because the diaphragm is low, the heart assumes a more vertical position, and secondly that the increased transverse diameter of the chest makes the cardio-thoracic ratio less. It will be shown later that we have been unable to confirm the latter assumption. The ptotic appearance of the heart was most evident in the asthmatic group, particularly in the cases classified as severe. In one severe case the cardiac shadow was so narrow that it scarcely extended beyond the lateral border of the vertebral bodies, and in only one (a moderate case) of the whole asthmatic group was the 'drop-like' appearance not evident. In patients

whose emphysema was due to other causes the ptotic heart was not so commonly seen, being present in only a quarter of the severe cases and a third of the moderate cases. When present, the ptotic appearance therefore suggests that the emphysema is due to asthma. When congestive cardiac failure supervenes, the heart becomes enlarged and the cardio-thoracic ratio is increased above the normal 1/2·00. Pulmonary heart failure was present in three of our cases, and these showed cardio-thoracic ratios of 1/1·64, 1/1·78, and 1/1·92. All the other cases (summarized in Table IV) showed reduced cardio-thoracic ratios. A small heart in a postero-anterior film is therefore good radiological evidence of emphysema if cardiac failure has not supervened. It will be seen

TABLE IV

Cardio-Thoracic Ratios

	Non-asthmatic		*Asthmatic*	
	Moderate	*Severe*	*Moderate*	*Severe*
Mean .	1/2·41	1/2·36	1/2·58	1/3·19
Range .	2·00–3·00	2·02–2·80	2·27–2·84	2·80–3·57

from Table IV that the cardio-thoracic ratio is less in asthmatic subjects than in those whose emphysema has other causes, and that in asthmatic subjects, but not in others, it is to some extent an index of the severity of emphysematous change. An area of translucency between the diaphragm and the heart shadow on the left side was seen in two-thirds of the cases we studied. It was marked in the severe asthmatic group, and was present in all but two of the moderately emphysematous patients whose disability resulted from asthma. In the groups whose emphysema resulted from other causes, it was seen in approximately two-thirds of the severe and two-thirds of the moderate cases. The presence of this radiological sign is therefore good evidence of emphysema, and when marked suggests an asthmatic origin. There seems little doubt that it is due to the low diaphragm, which permits intrusion of the emphysematous left lower lobe between it and the heart.

Parkinson and Hoyle (1937), in their study of 80 cases of emphysema, found radiological enlargement of the pulmonary conus in 41 per cent. and of the right ventricle in 20 per cent. In our series two-thirds of the patients showed enlargement of the pulmonary conus, and less than one-fifth showed enlargement of the right ventricle. Enlargement of the pulmonary conus was seen in all the asthmatic group except one severe case, but none of these patients showed any enlargement of the right ventricle. Of those whose emphysema was attributable to other causes, three-fifths of the severe and four-sevenths of the moderate cases showed enlargement of the pulmonary conus, and four (approximately one-quarter) of the severe cases and four (approximately one-fifth) of the moderate cases showed right ventricular enlargement. The presence of radiological cor pulmonale cannot, therefore, be regarded as having any material significance as regards the severity or aetiology of the emphysematous change, but enlargement of the pulmonary conus is sufficiently often

seen in emphysema to be good evidence of its presence where no other cause for the enlargement can be detected.

3. *The diaphragm.* (*a*) *Shape.* Flattening of the diaphragm has long been recognized as a valuable radiological indication of the presence of emphysema (Kerley, 1936; Rubin, 1936; Parkinson and Hoyle, 1937). It was present, and obvious in the postero-anterior film, in all our cases except one. In 14 cases the degree of flattening was asymmetrical, being greater on the right in 13 and on the left in one. Flattening was greater in severe than in moderate cases, but the difference between the two groups was insufficient for much reliance to be placed on the degree of flattening as an index of the severity of the emphysematous change. The one case in which the shape of the diaphragm appeared normal was assessed clinically as severe, and had a residual air / total lung-volume ratio of 56 per cent. In a few cases the diaphragm, besides showing a lack of upward convexity, sloped downwards like a tent from the midline, but this topographical feature had no aetiological significance. The costal insertions of the diaphragm were in some instances discernible in the radiograph, but this appearance was in no way correlated with the severity or aetiology of the emphysematous process.

(*b*) *Height.* In all our cases the diaphragm appeared low in postero-anterior radiographs and on screening. This appearance was more striking in the asthmatic patients than in those whose emphysema resulted from other causes, but it was not accurately related to the severity of ventilatory insufficiency. Many whose disability was relatively slight showed a lower diaphragm than did others who were severely dyspnoeic at rest. Details of the measured level of the diaphragm in normal subjects and in our cases of emphysema are given in paragraph 7 and Tables VIII (*a*) and (*b*).

(*c*) *Movement.* The range of movement of the diaphragm was noted in all cases. It was soon appreciated that bronchospasm affected diaphragmatic movement, and that patients screened during a severe asthmatic paroxysm showed an immobile diaphragm; but the asthmatic group as a whole had normal, or only slightly reduced, diaphragmatic excursion if screened when no bronchospasm was present. The subjects whose emphysema resulted from causes other than asthma presented a somewhat different picture. All the cases classified as severe showed gross restriction of movement, amounting in seven cases to virtual immobility, while one-half of the moderate group showed some diminution in respiratory excursion. In eight cases it amounted almost to immobility, while in another eight the range of movement was normal. All subjects with a normal diaphragmatic excursion would, in a further classification of the moderate subjects, have been regarded as mild cases, and only two had a residual air / total lung-volume ratio of over 50 per cent. In five patients diaphragmatic movement was unequal on the two sides, and in each case the right side showed the greater restriction. This asymmetry is no doubt related to the frequent asymmetry of the shape of the diaphragm mentioned above. We conclude that flattening, depression, and reduced respiratory excursion of the diaphragm is good radiological evidence of emphysema, and that in the absence of bronchospasm the degree of restriction of diaphragmatic movement

is an indication of the severity of emphysema and, if marked, suggests a non-asthmatic aetiology.

4. *Hilar movement.* In two-thirds of the subjects a downward movement of the hila was seen on inspiration. This phenomenon has been looked for in a large number of normal subjects, but has not been observed in any of them. It is therefore regarded as a valuable indication of the presence of emphysema. In most of the cases of emphysema in which it was not present, either the degree of emphysema was mild or the diaphragm was immobile. Some diaphragmatic movement appears essential for its production. It was seen equally in the asthmatic group and in the group of emphysema due to other causes. We have come to regard it as good evidence of the presence of emphysema if some diaphragmatic movement remains.

5. *Bullae and cysts.* Bullae which are visible radiologically are not common in emphysema. When present they are usually at the apices, and the question of tuberculous infection may arise and have to be excluded. Such bullae were only present in two of our cases, both classified as moderate and due to bronchitis. A severe case due to long-standing asthma, in a woman of 29 years, showed a large tension cyst at the right apex and five smaller cysts, all containing fluid, in the lower lobes; and a moderate case due to chronic bronchitis showed a large cyst of undetermined nature in the left lower lobe. The radiological presence of bullae and cysts usually serves to complicate rather than simplify the diagnostic problem, and does not appear to indicate the severity or origin of the emphysema.

6. *Kyphosis and 'apical rib crowding'.* Kyphosis is one of the physical signs classically associated with emphysema; it is, of course, well seen on lateral radiographs, and is indicated on posterio-anterior projection by 'apical rib crowding'. It was present in only one of the asthmatic group, but in patients whose emphysema had other causes it was seen in two-thirds of the severe and one-half of the moderate cases. Kyphosis is therefore some indication of the severity of the emphysematous process, and suggests that it has arisen from causes other than asthma.

7. *Radiological chest volume.* The radiological chest volume was determined in the usual way by measuring with a planimeter the area occupied by the heart and lungs in a postero-anterior chest radiograph and multiplying it by the anteroposterior diameter of the chest at the level of the fifth costal cartilage at full inspiration. The results obtained are summarized in Table V. Hurtado, Kaltreider, Fray, Brooks, and McCann (1934) found no difference between the mean radiological chest volume of 26 patients suffering from emphysema and that of 50 normal subjects, which is surprising in view of the generally held belief that the diaphragm is lowered and the anteroposterior diameter of the chest increased in emphysema. But the age, height, and weight of their two groups were grossly dissimilar, and we thought that this might account for their unexpected findings. We therefore noted the age and measured the radiological chest volume, height, and weight of 58 normal men and 31 normal women, and from the data thus provided calculated regression equations by which the

radiological chest volume of normal subjects could be predicted from age, height, and weight. The regression equations thus obtained were utilized to predict the normal radiological chest volume of each of our emphysematous subjects, and from Table V it will be seen that in each of our three large groups

TABLE V

Comparison of Mean Observed and Predicted Radiological Chest Volumes in Emphysema

Aetiological group	*Number and sex*	*Degree of severity*	*Observed volume (ml.)*	*Predicted volume (ml.)*	*Observed minus predicted volume (ml.)*	*Standard deviation of mean (ml.)*	*t*	*P*
Asthmatic	8 F	Moderate	12,612	10,247	+2,365	470	5·03	<0·001
Other causes	21 M	Moderate	16,382	14,535	+1,847	283	6·53	<0·001
	17 M	Severe	16,788	14,590	+2,198	315	6·98	<0·001

Prediction formulae. Males: R.C.V. = −12·877+0·037 age (years) +0·288 height (inches) +0·046 weight (pounds). Females: R.C.V. = −2·079+0·034 age (years) +0·143 height (inches) +0·020 weight (pounds).

the excess of the mean observed radiological chest volume over its mean predicted value was highly significant. The individual observed values were also significantly greater than the mean predicted values in approximately 40 per cent. of our patients.

We therefore conclude that in emphysema the radiological chest volume is increased. The next question is whether this increase results from an increase in the anteroposterior or transverse diameters of the chest, or from depression of the diaphragm, or from all three factors in varying proportion. To elucidate this question we next measured the anteroposterior diameter of the chest of each of the 58 normal men and 31 normal women mentioned above, and from these measurements calculated regression equations by which this diameter could be predicted from age, height, and weight. The equations thus obtained were used to predict the anteroposterior chest diameter of the patients with emphysema included in each of our three main groups; the results obtained, together with the observed measurements, are shown in Table VI. It will be seen that the increase in the anteroposterior diameter of the chest is highly significant in all the three emphysematous groups, but the values for t are all lower than those obtained for the radiological chest volume, showing that the increased anteroposterior chest diameter is partly, but not wholly, responsible for the increase in radiological chest volume in emphysema, and that diaphragmatic depression or increased transverse diameter of the chest must also play a part. To ascertain the extent to which the transverse diameter of the chest contributes to the increase in radiological chest volume in emphysematous subjects, we measured the maximum transverse diameter and the transverse diameter at the level of the fifth and eighth costal cartilage in the posteroanterior radiographs of all our cases of emphysema and in the radiographs of 100 normal subjects. It will be seen from Table VII that the transverse

diameter of the chest is unaffected by age, and that it is slightly smaller in patients suffering from emphysema than it is in normal subjects. Diaphragmatic flattening must therefore occur in emphysema, and together with the increase in the anteroposterior diameter of the chest accounts for the increase in radiological chest volume. To confirm this conclusion we next noted the level of the most medial part of the left diaphragm, in relation to the ribs posteriorly, in

TABLE VI

Comparison of Mean Observed and Predicted Anteroposterior Chest Diameters in Emphysema

Aetiological group	*Number and sex*	*Degree of severity*	*Observed diameter (inches)*	*Predicted diameter (inches)*	*Observed minus predicted diameter (inches)*	*t*	*P*
Asthmatic .	8 F	Moderate	8·34	7·66	0·68	4·30	<0·01
Other causes	18 M	Moderate	9·44	8·98	0·46	2·96	<0·01
	14 M	Severe	9·97	9·11	0·86	4·87	<0·001

TABLE VII

Comparison of the Transverse Diameter of the Chest in Normal and Emphysematous Subjects by Decennia

Group	*Sex*	*Level of measurements*	*Mean transverse diameter of thorax (inches) at age (years)*						
			10–19	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*All ages*
Normal .	M		$n = 5$	$n = 9$	$n = 9$	$n = 13$	$n = 16$	$n = 6$	$n = 58$
		5th costal cartilage	8·75	9·78	9·19	9·00	9·31	9·00	9·22
		8th " "	10·00	11·00	10·69	10·48	10·53	10·83	10·53
		Maximum	10·90	11·83	11·78	11·88	11·89	11·33	11·72
	F		$n = 10$	$n = 8$	$n = 6$	$n = 5$	$n = 7$	$n = 6$	$n = 42$
		5th costal cartilage	8·78	9·06	8·71	8·25	8·68	7·75	8·60
		8th " "	9·80	10·38	9·83	9·50	10·17	8·83	9·38
		Maximum	10·23	11·13	10·29	10·20	10·96	9·54	10·23
Emphysema	M		..	..	$n = 2$	$n = 11$	$n = 14$	$n = 9$	$n = 36$
		5th costal cartilage	..	..	9·25	9·30	9·08	9·18	9·17
		8th " "	..	..	10·13	10·38	10·15	10·08	10·20
		Maximum	..	..	10·88	11·30	11·33	11·18	11·25
	F		$n = 1$	$n = 3$	$n = 3$	$n = 4$	$n = 1$	..	$n = 12$
		5th costal cartilage	9·50	8·50	9·00	8·69	8·25	..	8·75
		8th " "	10·00	9·17	9·67	9·25	10·00	..	9·45
		Maximum	10·00	9·42	10·08	9·50	10·75	..	9·77

our patients with emphysema and 200 normal subjects. The results obtained are shown in Tables VIII (*a*) and (*b*), from which it will be seen that in normal subjects the rib level of the diaphragm is unaffected by age, and that in the victims of emphysema this level is the same as in health. It is therefore clear that the low appearance of the diaphragm in emphysema results from flattening and hypertonicity, and we are unable to confirm the statement of Kerley (1936) that the diaphragm is 'one rib interspace lower' in emphysema than in normal subjects. Put in another way, the elevation of the costal attachments of the diaphragm, due to the increased anteroposterior diameter, seems to be about

equal in magnitude to the flattening of the diaphragm, so that its level in relation to the ribs is unaltered.

TABLE VIII (*a*)

Mean Rib Level of Diaphragm in 100 Normal Subjects by Decennia

Sex		*Age (years)* 10–19	20–29	30–39	40–49	50–59	60–69	*All ages*
M	Number	5	9	9	13	16	6	58
	Rib level	11·50	11·61	11·56	12·00	11·53	11·83	11·68
F	Number	10	8	6	5	7	6	42
	Rib level	11·35	11·50	11·75	11·70	11·64	11·25	11·51

TABLE VIII (*b*)

Comparison of Mean Rib Level of Diaphragm in Normal and Emphysematous Subjects

Group	*Number*	*Rib level*
Normal	200	11·62
Emphysema	49	11·79

8. *'High' maximum transverse thoracic diameter.* The presence of a 'high' maximum transverse thoracic diameter is recognized as good radiological evidence of the presence of emphysema. To ascertain the validity of this belief we have compared the posterior rib-level of the maximum transverse thoracic diameter in 100 normal subjects with that found in our patients with emphysema. The results obtained are shown in Table IX, from which it will be seen

TABLE IX

Mean Rib Level of Maximum Thoracic Width in Normal and Emphysematous Subjects by Decennia

Group	*Sex*	*Age (years)* 10–19	20–29	30–39	40–49	50–59	60–69	*All ages*	*Diaphragmatic level (all ages)*
Normal	M	$n = 5$ 11·5	$n = 9$ 11·3	$n = 9$ 11·3	$n = 13$ 11·9	$n = 16$ 11·6	$n = 6$ 11·8	$n = 58$ 11·6	$n = 58$ 11·7
	F	$n = 10$ 11·1	$n = 8$ 11·4	$n = 6$ 11·8	$n = 5$ 11·4	$n = 7$ 11·5	$n = 6$ 11·3	$n = 42$ 11·4	$n = 42$ 11·5
Ephysema	M			$n = 2$ 11·0	$n = 11$ 11·1	$n = 14$ 11·4	$n = 9$ 11·4	$n = 36$ 11·3	$n = 36$ 11·8
	F	$n = 1$ 7·0	$n = 3$ 9·7	$n = 3$ 10·2	$n = 4$ 8·3	$n = 1$ 11·0		$n = 12$ 9·2	$n = 12$ 11·8

that the maximum transverse diameter in normal male and female subjects and in male emphysematous patients is at virtually the same level as the diaphragm. In the female emphysematous patients, however, the mean maximum transverse diameter is over two and a half rib spaces higher than the mean diaphragmatic level. As most of our female patients belonged to the asthmatic

group, this finding suggested that the high transverse diameter was the result of asthma. Individual study, however, showed that it was also present in two of the three female patients whose emphysema resulted from other causes; but the only male who showed a high maximum transverse diameter was a severe asthmatic. We conclude that the high transverse diameter in emphysema tends to develop in the female rather than in the male, and when present points to an asthmatic origin. In view of the lower age distribution of the female subjects in our series, it is possible that comparative youth is also a factor in the production of this change.

9. *Costal cartilage calcification.* The majority of medical text-books mention premature calcification of the costal cartilages as a feature of emphysema. We therefore compared the radiological state of the costal cartilages in 200 normal subjects, drawn about equally from each decade from 10 to 70 years of age, with that seen in our cases of emphysema. As we expected, the normal group showed that costal cartilage calcification is largely dependent on age, and from the results obtained we were able to predict the number of our patients with emphysema who would have showed costal cartilage calcification had they been normal subjects. These predicted figures and the observed figures in emphysema, shown in Table X, were not significantly different, and we conclude that premature costal cartilage calcification is not a peculiarity of emphysema.

TABLE X

Predicted and Observed Costal Cartilage Calcification in Emphysema (Age Standardized)

	Male patients		*Female patients*	
	With	*Without*	*With*	*Without*
Predicted	25	13	4·4	5·6
Observed	28	10	2	8

We are indebted to Dr. H. Black and Professor L. Hogben for placing the facilities of their departments at our disposal, to Mr. A. C. Pincock for valuable technical advice and assistance, and to Imperial Chemical Industries for a grant towards the expenses of this investigation.

Summary

1. Fifty-two cases of emphysema have been assessed clinically, spirometrically, and radiologically in an endeavour to ascertain the correlation between the radiological appearances and the clinical state.

2. All patients showed some radiological abnormalities, the most constant being depression and flattening of the diaphragm. These features are not accurately related to the severity of the disease, and, in the absence of bronchospasm, restriction of the respiratory excursion of the diaphragm appears to be the most valuable radiological index of the degree of emphysema.

3. Over-translucency of the lung fields is usually present in emphysema, but

may be obscured by a variety of factors. The relative brilliancy of the lung bases, and the translucency and area of the retrocardiac and anterocardiac windows, are more important guides than the general translucency of the lung fields on postero-anterior films. Marked over-translucency indicates an asthmatic origin.

4. The heart is usually small in posterio-anterior radiographs of emphysematous subjects, and the cardio-thoracic ratio is reduced. A gap is frequently visible between the diaphragm and the left ventricle. These changes are, we believe, entirely due to the low diaphragm, and are most marked in asthmatic subjects, in whom they can be regarded as some guide to the severity of the emphysematous change in the lungs. On screening, the pulmonary conus was seen to be enlarged in two-thirds, and the right ventricle in one-fifth, of the cases, but the presence of radiological cor pulmonale has no significance as regards the severity or aetiology of the emphysema. If pulmonary heart failure supervenes the cardiac silhouette becomes generally enlarged.

5. Hilar descent on inspiration is a valuable radiological sign of emphysema, but when the diaphragm becomes immobile it is no longer evident.

6. Kyphosis is often seen, and suggests a non-asthmatic aetiology. Its presence is some indication of the severity of the emphysema.

7. The radiological chest volume is increased in emphysema as a result of diaphragmatic depression and increase in the anteroposterior diameter of the chest. It is of little value as an index of severity. The transverse diameter of the chest is not increased in emphysema, and the rib-level of the diaphragm is the same in emphysema as in normal subjects. The low diaphragm is therefore a visual impression, and does not lend itself to rapid quantitative assessment.

8. In some cases of emphysema the maximum transverse diameter of the chest is at a level considerably higher than the diaphragm. Such a finding suggests an asthmatic aetiology and is most commonly seen in female patients, but the age of onset of respiratory disease may also be a factor.

9. Premature calcification of the costal cartilages is not a feature of emphysema.

10. Though the presence of emphysema can be readily detected radiologically, and though radiography may be invaluable in ascertaining the cause of the emphysematous change, the degree of emphysema can be much more accurately assessed clinically and spirometrically than radiologically. The respiratory excursion of the diaphragm is the most valuable radiological guide to the severity of emphysema.

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THE MECHANISM AND SIGNIFICANCE OF THE COLD PRESSOR RESPONSE[1]

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Since its introduction by Hines and Brown in 1932 the cold pressor test has been used by several authors in the study of hypertension. The test is based on the fact that immersion of a hand in ice-cold water causes a rise of blood-pressure which varies in size in different subjects (Hines and Brown, 1932). It was designed to measure the reactivity of the blood-vessels to a standard stimulus. The technique adopted by Hines is as follows (Hines and Brown, 1933; Hines, 1939; Hines, 1940*a*). The subject is rested in the supine position until the blood-pressure has reached a steady basal level. The hand on the side opposite to the arm used to record the blood-pressure is then immersed in water at a temperature of 4° C. for one minute. The rise of blood-pressure is measured by taking readings 30 to 60 seconds after the beginning of immersion. After the end of cooling a few further readings are taken until the pressure has fallen to its original basal level. The maximum increase of the systolic and diastolic blood-pressures above the basal level is taken as a measure of the size of the cold pressor response. On the basis of results obtained on 1,015 normal subjects and 841 subjects with essential hypertension Hines (1940*a*) made several claims regarding the significance of the cold pressor test. He found that over 95 per cent. of hypertensive subjects, but only 15 per cent. of normal subjects, gave large or 'hyperreactive' cold pressor responses. Although Hines and Brown (1933) had originally suggested that a systolic or diastolic response of 15 mm. of mercury or more should be regarded as an excessive or 'hyperreactive' response, they later raised this arbitrary limit to 22 mm. (Hines and Brown, 1936). Hines (1939, 1940*a*) ultimately defined an excessive response as one in which the systolic rise exceeds 20 mm. and the diastolic rise exceeds 15 mm. of mercury. Smaller responses were regarded as normal or 'hyporeactive'. Since by these criteria almost all his subjects with essential hypertension gave excessive responses, Hines concluded that such a response is a characteristic feature of essential hypertension (Hines and Brown, 1933, 1936; Hines, 1940*a*). The only two cases of hypertension due to nephritis which were tested by Hines and Brown (1933) gave small responses. Hines suggested further that an excessive response in a normal subject indicates a constitutional predisposition to

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essential hypertension, and that only those normal subjects who give such responses can develop this disorder.

Subsequent authors have been unable to confirm several of these claims. Figures published by Briggs and Oerting (1933) show that most of their hypertensive subjects gave small cold pressor responses according to the criteria used by Hines (1940*a*). The mean diastolic response of their hypertensive cases was actually smaller than that of their normal controls. According to Ayman and Goldshine (1938) the mean value of the cold pressor responses of a group of 88 hypertensive subjects was larger than that of a group of 48 normal controls, but their results were very variable on repetition of the test in the same subject. Alam and Smirk (1938), using a modified technique of applying the test, found that there was considerable overlap between the size of the responses of normal and of hypertensive subjects. They agreed with Hines in finding that subjects with hypertension due to chronic nephritis had, on an average, smaller responses than those with essential hypertension. Miller and Bruger (1939) came to the same conclusion, but other observers have reported large cold pressor responses in several subjects with hypertension due to chronic nephritis (Ojeda and Sepulveda, 1942). Reisinger (1941) found that only 73 per cent. of subjects with essential hypertension, and as many as 50 per cent. of normal subjects, studied by him were hyperreactors. Pickering and Kissin (1936) and Todd (1944) observed no significant difference between the responses of their normal and hypertensive subjects, provided they were of comparable age. Those of the above observers who were unable to confirm the view that all, or almost all, subjects with essential hypertension have excessive responses, relied for the diagnosis of hypertension on such a generally accepted criterion as a raised basal blood-pressure with or without cardiac enlargement. It appears that Hines was prepared to make a diagnosis of hypertension solely on the basis of a raised casual blood-pressure (Hines and Brown, 1936). There is some evidence that large cold pressor responses are more frequent in subjects who react with large temporary elevations of blood-pressure to the stress of an unaccustomed medical examination than in subjects whose blood-pressure is less labile in such circumstances (Hines, 1940*a*; Thacker, 1940; Russek and Zohman, 1945). While subjects with the more labile blood-pressure may be more likely to develop hypertension in the future than those with the less labile pressure (Hines, 1940*b*), it is essential, in a comparative study of the size of the cold pressor responses of normal and hypertensive subjects, only to include cases of undoubtedly established hypertension in the hypertensive group. By classifying many subjects with normal basal but elevated casual blood pressures as hypertensive, Hines may have increased the proportion of hyperreactors in his so-called hypertensive group. By the same process of selection the proportion of hyperreactors among the remaining normal subjects would have been correspondingly reduced. This may account for some of the discrepancies between the results of Hines and other authors.

Unlike Hines and Brown (1933, 1936) many observers have been unable to obtain consistent results with the cold pressor test on repetition in the same

subject (Ayman and Goldshine, 1938; Reid and Teel, 1938; Chesley and Chesley, 1939; Reisinger, 1941; Goldring and Chasis, 1944). Several of these observers found the results to be so variable that the same subject appeared to be a hyperreactor on one day and a hyporeactor the next. In some subjects the blood-pressure dropped during the cold immersion instead of showing the usual rise. Such falls were associated with faintness, which was presumably due to the severe pain associated with the cold immersion (Randall, Murray, and Mussey, 1935; Bak, 1937; Brada and Feil, 1937; Reid and Teel, 1938; Ayman and Goldshine, 1938). The size of the cold pressor response is also affected by the age of the individual, and increases with advancing years in normal and in hypertensive subjects (Pickering and Kissin, 1936; Alam and Smirk, 1938; Hines, 1940*a*; Russek, 1943; Russek and Zohman, 1945). The proportion of hyperreactors in the normal population actually increases in the later age groups (Feldt and Wenstrand, 1942; Russek, 1943; Russek and Zohman, 1945). According to Russek (1943), 24 per cent. of 62 normal subjects between the ages of 40 and 49 years, and 56 per cent. of 57 subjects between 60 and 69 years, were hyperreactors. The rise in the incidence of hyperreactors with age in the normal population provides a strong argument against Hines' hypothesis that hyperreaction is a constitutional characteristic present from childhood onwards (Hines, 1937*a*) and only found in subjects suffering from, or predisposed to, essential hypertension. If this theory were correct, the proportion of hyperreactors in the normal population should decrease with age; for with advancing years an increasing number of hyperreactors should have developed hypertension, leaving a decreasing proportion of hyperreactors in the remaining normal population (Yates and Wood, 1936). The reverse is in fact the case.

The only direct evidence presented by Hines and Brown (1936) in support of the claim that an excessive cold pressor response indicates a pre-hypertensive state is also unconvincing. They followed up three subjects from 1932 to 1935. These subjects had normal blood-pressures and excessive cold pressor responses in 1932, and were said to have developed hypertension three years later. The diagnosis of hypertension on this occasion was made solely on the basis of raised casual blood-pressures, while the basal pressures recorded after the short period of rest preceding the cold immersion were normal, being 130/80 mm. of mercury in two cases and 128/75 mm. in the third. Hines (1940*a*) also stated that 38 per cent. of 24 subjects who, in 1933, had had normal blood-pressures with excessive cold pressor responses, had developed hypertension six years later, while none of 42 subjects with small cold pressor responses had become hypertensive during the same period. The relevant data were not given, and no information was available as to one-third of the 42 subjects with small responses. Armstrong and Rafferty (1950) found no correlation between the size of the systolic cold pressor response and the increase of basal blood-pressure over a period of seven years in a follow-up study of 166 Air Force officers. The strongest argument put forward by Hines in favour of regarding a large cold pressor response as an indication of a pre-hypertensive state is the fact that he found a much higher incidence of a family history of hypertension among normal

subjects with large than among those with small cold pressor responses (Hines and Brown, 1935; Hines, 1937*b*). Of 492 normal subjects with small responses only 17·2 per cent. gave a family history of hypertension, while 84·2 per cent. of 116 normal subjects with large responses gave such a history. Dieckmann and Michel (1935) and Briggs and Oerting (1937) are the only observers who have agreed with these findings. Chesley and Chesley (1939) found no correlation between a family history of hypertension and the size of the cold pressor response in a study of 534 women, and all other observers are in agreement with their negative findings (Pickering and Kissin, 1936; Reid and Teel, 1938; Feldt and Wenstrand, 1942; Russek, 1943; Todd, 1944). As there is considerable evidence that essential hypertension has a hereditary basis (Platt, 1947), these negative results suggest that a hyperreaction in a normal subject is in fact not related to a liability to future hypertension. The fact that many observers have not been able to confirm the claim that all, or almost all, subjects with essential hypertension have large cold pressor responses, and the fact that such responses are found in half the normal population over 50 years of age (Russek, 1943), are of course further reasons against regarding large responses to the cold pressor test as an indication of a pre-hypertensive state.

The Present Study

The review of the literature given above shows that different observers who have used the cold pressor test have obtained conflicting results, and that the claims made by Hines (1940*a*) have in general not been confirmed. The question therefore arises, what determines the height of the cold pressor response in an individual subject, and what significance, if any, can be attached to the results obtained with this test? There is considerable evidence that the rise in blood-pressure during cold immersion is due to vasoconstriction of sympathetic origin (Hines and Brown, 1933; Wolf and Hardy, 1941; Reiser and Ferris, 1948), but the exact nature of the stimulus responsible for this widespread vasoconstriction is still under discussion. Hines and Brown (1936) were naturally aware of the fact that the immersion of the hand in ice-cold water is accompanied by pain. Although the amount of pain differed from subject to subject, some being only slightly disturbed, whereas in others the intensity of the pain limited the duration of cooling, they thought that the size of the cold pressor response was unaffected by the severity of the pain. In their opinion the vasoconstriction was of purely reflex origin, and occurred in direct response to the stimulation of sensory nerve-endings in the immersed hand. Most other observers have emphasized the close relationship between the pain experienced during the cold immersion and the size of the pressor response (Briggs and Oerting, 1933; Dieckmann and Michel, 1935; Pickering and Kissin, 1936; Reid and Teel, 1938; Ayman and Goldshine, 1938; Reisinger, 1941; Wolf and Hardy, 1941; Russek, 1943). Wolf and Hardy (1941), in a quantitative study of the relationship between pain and rise of blood-pressure during cold immersion of one hand, showed that in an individual subject the amount of pain experienced is greater

the lower the cooling temperature used, and that the increase of blood-pressure varies directly with the amount of pain. Those subjects who complained most severely of pain had the largest cold pressor responses. Wolf and Hardy concluded that the rise of blood-pressure during cold immersion is due to, and quantitatively determined by, the subject's reaction to the pain. In this connexion it is of interest to note that McMurray (1950) has recently shown that in a woman with complete insensitivity to painful stimuli since birth, cold immersion at 0° C. to 2° C. was accompanied neither by pain nor by a rise of blood-pressure.

The observations of Wolf and Hardy do not, however, necessarily disprove the suggestion that the increase of blood-pressure is due to a purely reflex vasoconstrictor response (Hines and Brown, 1936). It is theoretically possible that the afferent impulses responsible for the rise of blood-pressure during cold immersion ascend in the central nervous system to excite a vasomotor reflex at some level below that at which pain is perceived, in other words, below the sensory thalamus, while the impulses responsible for pain ascend to a higher level. If this were the case, the size of the pressor response would vary with the amount of pain not because the pain causes the rise of blood-pressure, but because both are initiated by the same peripheral stimulus. That nocuous stimulation of peripheral nerves can cause a rise of blood-pressure in the absence of sensation (Ranson, 1921) was demonstrated by Sherrington (1906) in spinal animals, and again recently by Gordon (1943) in decerebrate and anaesthetized animals. In man it has been shown by Guttmann and Whitteridge (1947) that distension of the bladder causes a rise of blood-pressure even in patients with complete transection of the spinal cord in the cervical or upper thoracic region. There is also evidence that in man an infrathalamic reflex may be responsible for the vasoconstriction which may occur in response to peripheral stimuli (Marquis and Williams, 1938). These authors relied on plethysmographic studies, and did not record the blood-pressure. It has been shown that the cold pressor response cannot be elicited from the anaesthetic legs of patients with transection of the spinal cord in the lower thoracic or lumbar region (Sullivan, 1941; Todd, 1944) or from the analgesic hand of a patient with syringomyelia (Garai, 1945). The latter finding suggests that the afferent impulses responsible for the rise of blood-pressure during cold immersion depend on intact pain- and temperature-conducting pathways in the spinal cord, but no information is available about their conduction paths above the cervical region. If these impulses travel in the spinal cord in close association with the spinothalamic tract, but separate from it at or below the thalamus to excite a vasopressor reflex, as has been suggested by Kunkle and Chapman (1943), neurological lesions interrupting these pathways below the thalamus would abolish the cold pressor response as well as pain sensation, but in patients with lesions above this level it should still be possible to elicit cold pressor responses, even if the lesion has resulted in loss of pain-perception. If, however, the rise of blood-pressure occurs only in response to the perception of pain, the response should be abolished by lesions interrupting the pathways concerned with pain-sensation at all levels of the nervous system,

and also by anaesthesia of hysterical origin. In order to decide whether the cold pressor response is the result of a reflex whose central connexions are complete below the thalamus, or whether it is dependent on pain-perception, observations have been carried out on patients with unilateral analgesia due to cerebral vascular lesions probably involving the internal capsule and in patients with hysterical anaesthesia. It will be shown that in these subjects the cold pressor response could not be obtained from the anaesthetic limbs, and that pain-sensation is essential for the production of the cold pressor response.

Method

Three cases of hemianaesthesia due to cerebral vascular lesions and six cases of hysterical anaesthesia were studied. Two patients with analgesia due to syringomyelia and one with a peripheral nerve lesion were also investigated. The subjects were selected because of their profound loss of sensation. Since the object of the experiments was to determine whether cold pressor responses could be elicited from anaesthetic limbs, the strongest possible cold stimulus was used. Cold immersion was carried out in a mixture of ice and water at 0° C. The mixture was stirred frequently throughout the experiment. When the test was applied to a hand, four fingers only were immersed, as it was anticipated that in some of the cases complete anaesthesia might be confined to a few fingers. When the test was applied to a foot, the whole foot was immersed sufficiently to cover all the toes. Immersion was continued for at least three minutes, because preliminary investigations had shown that the maximum increase of blood-pressure was sometimes not reached until three minutes from the beginning of cold immersion. If no blood-pressure response had occurred after three minutes, cooling was continued for five or ten minutes. Immersion of a normally sensitive extremity for longer than three minutes could rarely be tolerated on account of the severe pain, and was unnecessary because the maximum rise of blood-pressure had always occurred by this time. It was clearly essential to avoid rises of blood-pressure due to apprehension. The subjects were therefore made to sit or lie down comfortably with their eyes shut, and they were told that after some time the fingers of one hand, and later those of the other hand, and in some cases a foot, would be lifted by the experimenter and immersed in water. They were told that the water might be warm or cold, but no mention was made of pain or discomfort. After these preliminary explanations the blood-pressure was recorded frequently until a steady basal level had been reached. Before immersion in cold water, the effect on the blood-pressure of immersion in comfortably warm water at 37° C. was observed. Thereby blood-pressure responses due to apprehension at the moment of immersion could be assessed and excluded. In some subjects immersion at 37° C. had no effect on the blood-pressure. In these cases the limb was taken out again after a few minutes, and after a further interval of several minutes the same limb was immersed at 0° C. If the first immersion at 37° C. had produced a rise of blood-pressure, it was repeated one or more times. The subject became accustomed

to these repeated immersions at 37° C., so that on the second or third occasion the blood-pressure remained unchanged. When this was the case the fingers, or a foot, were next immersed at 0° C. The subject, with his eyes shut, was unaware whether the limb was about to be immersed in warm or cold water. Any increase of blood-pressure during the cold immersion was therefore due to the sudden cooling. The anaesthetic limb was always immersed first, and the whole procedure was then repeated on the opposite (normal) side, if the sensory loss was unilateral. If both hands or both feet were anaesthetic, one of the anaesthetic limbs was tested first, and subsequently a normal hand or foot.

TABLE I

Cold Pressor Responses Elicited from Opposite Limbs in Three Normal Subjects

Four fingers or a foot were immersed at 0° C. for three minutes.

Experiment	*Extremity immersed*	*Maximum rise of blood-pressure (mm. Hg)*	
		systolic	*diastolic*
1	R. fingers	19	24
	L. fingers	21	25
	R. foot	37	46
	L. foot	30	44
2	R. fingers	18	26
	L. fingers	22	28
	R. foot	37	32
	L. foot	34	32
3	R. fingers	15	16
	L. fingers	12	16
	R. foot	16	12
	L. foot	16	14

Results

Table I summarizes the results obtained in three normal control subjects. In these the responses elicited from opposite hands, or from opposite feet, were nearly equal. In experiments 1 and 2 the subjects complained of greater pain during immersion of the feet than of the fingers, and the cold pressor responses elicited from the feet were correspondingly larger than those elicited from the fingers. In experiment 3 there was no obvious difference in the severity of the pain felt during immersion of the feet as compared with the fingers, and the cold pressor responses were of similar size. Table II gives the results obtained in subjects with anaesthesia due to neurological lesions, and Table III gives the results obtained in patients with hysterical anaesthesia. The results can be summarized briefly by saying that whenever anaesthesia was complete, so that no pain was felt during cold immersion, no significant rise of blood-pressure occurred, whereas a rise in blood-pressure and pain invariably accompanied cold immersion of a normally sensitive extremity. This was the case both when the anaesthesia affected all modes of sensation and was due to a peripheral nerve lesion (experiment 4), and when it affected pain- and temperature-sensation only, as in the cases of syringomyelia affecting the cervical and thoracic portions

TABLE II

Cold Pressor Responses in Subjects with Analgesia due to Lesions of the Central Nervous System

Case number	*Experiment*	*Diagnosis*	*Extremity immersed*	*Maximum rise of blood-pressure (mm. Hg)*	
				systolic	*diastolic*
1	4	Peripheral nerve lesion due to leprosy	Anaesthetic R. fingers	2	1
			Normal L. fingers	20	27
2	5	Syringomyelia	Anaesthetic (pain and temperature only) R. fingers	0	2
			Normal L. fingers	32	26
3	6	Syringomyelia	Anaesthetic (pain and temperature only) L. fingers	1	2
			Normal L. foot	21	16
4	7	Hemiplegia and hemianaesthesia due to cerebral vascular lesion	Anaesthetic R. fingers	7	2
			Normal L. fingers	60	44
5	8	Hemiplegia and hemianaesthesia due to cerebral vascular lesion	Anaesthetic L. fingers	3	4
			Normal R. fingers	15	13
6	9	Hemiplegia and hemianaesthesia due to cerebral vascular lesion	Anaesthetic (partial) R. fingers	14	10
			Normal L. fingers	26	20

TABLE III

Cold Pressor Responses in Subjects with Hysterical Anaesthesia

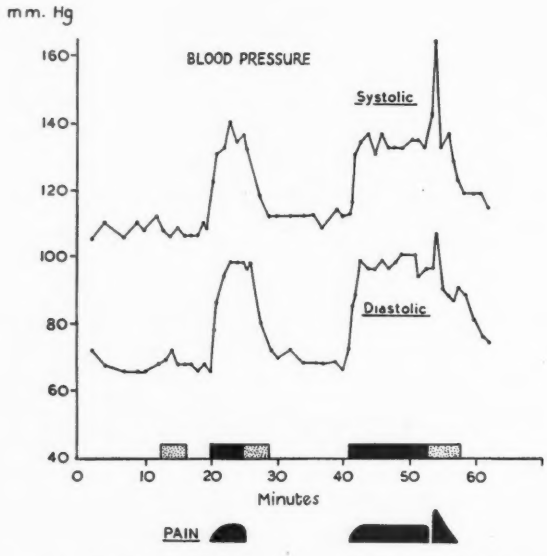
Case number	*Experiment*	*Diagnosis*	*Extremity immersed*	*Maximum rise of blood-pressure (mm. Hg)*	
				systolic	*diastolic*
7	10	Hysterical hemianaesthesia (left)	Anaesthetic L. fingers	4	2
			Normal R. fingers	20	24
8	11	Hysterical anaesthesia of L. leg	Anaesthetic L. foot	1	2
			Normal R. foot	18	12
9	12	Hysterical hemianaesthesia (left)	Anaesthetic L. fingers	4	2
			Normal R. fingers	15	12
10	13	Hysterical anaesthesia of R. arm	Anaesthetic R. fingers	0	2
			Normal L. fingers	14	8
11	14*a*	Hysterical anaesthesia of both arms and legs	Anaesthetic L. foot	1	4
			Anaesthetic L. fingers	1	3
	14*b*	After recovery	Normal L. foot	10	10
			Normal L. fingers	8	8

of the spinal cord (experiments 5 and 6). It also applied to those patients in whom a cerebral vascular lesion had resulted in complete hemianaesthesia (experiments 7 and 8) and to those in whom the anaesthesia was of hysterical origin (experiments 10 to 14). In Case 6 the hemianaesthesia, which was probably due to a vascular lesion in the internal capsule, was incomplete, so that some pain was felt during immersion of the affected fingers. This pain was accompanied by a smaller cold pressor response than that obtained during the considerably more painful immersion of the fingers of the opposite (normal) hand (experiment 9). In Case 11 the hysterical anaesthesia affected all four limbs, so that the subject was unaware of pain or cold during the immersion, and no cold pressor responses could be elicited (experiment 14*a*). After treatment by suggestion and psychotherapy sensation returned, and small but definite pressor responses accompanied the pain which was now felt during cold immersion (experiment 14*b*).

Discussion

These results show clearly that the cold pressor response is dependent on pain-perception, and is not due to an infrathalamic reflex. The response is abolished not only if pain-sensation is lost owing to a peripheral nerve lesion or a lesion in the spinal cord, but also if there is hemianaesthesia due to a cerebral vascular lesion. Even if there is no organic lesion, but pain is not felt as the result of a hysterical disturbance, the cold pressor response is lost. The latter finding is in conflict with results obtained by Cable and Smirk (1941) and Sullivan (1944) in cases of hysterical anaesthesia. The former observers found a rise of blood-pressure during the application of blocks of ice to an anaesthetic extremity, kept ischaemic by circulatory occlusion, in a woman with hysterical sensory loss. The latter found, in four cases of unilateral hysterical anaesthesia, that immersion of the affected limb in ice-cold water caused a small rise of blood-pressure which was of similar size to that obtained from the opposite (normal) limb. Neither of these authors carried out control observations by immersing the limbs in comfortably warm water, or by applying warm objects to the limb instead of blocks of ice. In several of the present experiments immersion of a normal, or of an anaesthetic hand or foot in water at 37° C. was accompanied by a rise of blood-pressure, which varied from 6 mm. to 15 mm. of mercury systolic and from 4 mm. to 8 mm. of mercury diastolic, and which could be abolished by repeating the immersion. Todd (1944) made similar observations in normal subjects. It is clear therefore that apprehension at the moment of immersion can raise the blood-pressure. Such responses of emotional origin must be excluded before the view is accepted that cold pressor responses can be obtained from anaesthetic limbs. When responses due to apprehension are prevented by repeated preliminary immersion in comfortably warm water at 37° C., as in the present observations, it becomes clear that no cold pressor responses can be elicited from anaesthetic limbs even if the anaesthesia is of hysterical origin. The close association between the pain and the blood-pressure response is illustrated further by the observation that in several experiments

on normal subjects, in whom cooling at 0° C. was continued for periods up to 20 minutes, pain persisted and the blood-pressure remained elevated throughout the cooling period. If, after cooling at 0° C. for 10 minutes or longer, the fingers are suddenly transferred into water at 37° C., the sudden rewarming is accompanied by very severe throbbing pain (Lewis, 1933), and this is accompanied by



The changes in pain and blood-pressure during cooling and sudden rewarming of the fingers in a normal subject. Stippled rectangles indicate immersion of four fingers in water at 37° C., and black rectangles indicate immersion at 0° C. Cooling at 0° C. for five minutes (20th to 25th minute) gave rise to pain and an increase of blood-pressure. Subsequent transfer into water at 37° C. caused the pain to subside and the blood-pressure to fall. Cooling at 0° C. for 12 minutes (41st to 53rd minute) again caused pain and a persistent rise of blood-pressure. Subsequent rewarming at 37° C. caused additional pain, which was accompanied by a further rise of blood-pressure. When the pain subsided the blood-pressure again returned to the basal level.

a further rise of blood-pressure even beyond the level reached during the period of continued cooling. As soon as the pain subsides the blood-pressure returns to its original basal level. The Figure presents the record of a typical experiment, and illustrates the relationship between the blood-pressure and the pain during cooling and sudden rewarming. The quantitative relationship between the pain and the rise of blood-pressure (Wolf and Hardy, 1941) is illustrated by the fact that in the two experiments on normal subjects (experiments 1 and 2) in whom pain was more severe with cooling of the feet than with cooling of the fingers, the greater pain was accompanied by correspondingly larger pressor responses. In the subject with partial hemianaesthesia due to a vascular lesion (experiment 9) in whom less pain was felt during cooling of the affected than of the normal fingers, the pressor response was correspondingly smaller. Since the size of the cold pressor response varies with the severity of the pain experienced during the

test procedure, and since the reaction of a subject to the same painful stimulus can vary considerably from time to time (Wolff and Hardy, 1947), it is not surprising that several authors have obtained variable results with the cold pressor test. Todd (1944) showed that the response may diminish if the test is repeated at short intervals. This is presumably due to the fact that the subject gets accustomed to the discomfort of the test procedure, so that the pain experienced, and hence the size of the response, diminishes on repetition. Even in dogs the size of the response decreases on repetition (Thomas and Warthin, 1940). The subject's mental attitude at the time of the test may also affect the size of the response (Wolf, Pfeiffer, Ripley, Winter, and Wolff, 1948).

It remains to consider the possible significance of the cold pressor test in relation to essential hypertension. Hines (1940*a*) claimed that large cold pressor responses are characteristic of subjects predisposed to, or suffering from, essential hypertension. Since it has been shown that the size of the response is determined by the subject's reaction to the pain associated with the test procedure, Hine's findings would suggest that pre-hypertensive and hypertensive subjects react more severely than normal subjects to a standard painful stimulus. This would lend support to the view that essential hypertension arises in subjects who react with an abnormal amount of tension and anxiety, and hence with abnormally large or prolonged increases of blood-pressure, to the various stresses experienced during life (Alexander, 1939; Wolf, Pfeiffer, Ripley, Winter, and Wolff, 1948). But in view of the fact that most other authors have found a smaller incidence of large cold pressor responses in hypertensive subjects, and a higher incidence in normal subjects, than was observed by Hines, it is at present not justifiable to conclude that an excessive reaction to painful stimuli is confined to, or is a constant characteristic of, hypertensive or pre-hypertensive subjects. Large responses may be somewhat more frequent among hypertensive than normal subjects, but the claim that the cold pressor test can be used to detect subjects likely to develop essential hypertension has not been confirmed. In so far as the test provides a measure of a subject's sensitivity to pain, it is suggested that it may be of value in further research on the subject of pain rather than of hypertension.

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Summary

1. The literature dealing with the applications of the cold pressor test to the study of essential hypertension is reviewed. It is pointed out that, on the evidence at present available, the claim that large cold pressor responses are

characteristic of subjects predisposed to, or suffering from, essential hypertension (Hines, 1940*a*) cannot be accepted.

2. Attention is drawn to the close association between the size of the cold pressor response and the severity of the pain experienced during the cold immersion (Wolf and Hardy, 1941).

3. It is shown that if pain-sensation is lost as the result of a peripheral nerve lesion or of syringomyelia, or if there is hemianaesthesia from a cerebral vascular lesion, the cold pressor response can no longer be elicited from the anaesthetic extremity.

4. Even if, without an organic lesion, pain is not felt during the cold immersion as the result of hysterical anaesthesia, the cold pressor response is abolished.

5. It is concluded that the vasoconstriction underlying the cold pressor response is not the result of a reflex, but that it occurs only in response to the pain experienced during the cold immersion. The cold pressor test provides a measure of sensitivity to a standard painful stimulus rather than of vascular reactivity.

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THE ASSOCIATION OF RAYNAUD'S PHENOMENA, CHRONIC HAEMOLYTIC ANAEMIA, AND THE FORMATION OF COLD ANTIBODIES[1]

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Three patients are reported in the present paper suffering from Raynaud's phenomena and chronic haemolytic anaemia. Haemoglobinuria on exposure to cold undoubtedly occurred in two of them, and its occurrence can be presumed with some probability in the third. Their sera contained cold agglutinins, cold haemolysins, and incomplete cold antibodies in considerable titre. The disorder is of unknown aetiology. An analysis is made of nine similar cases from the literature. Though minor serological differences between the cases have been noted, the similarities are very striking, and it is considered that the group deserves wider recognition.

Case Reports

Case 1

A married woman, aged 61 years, employed as a cook at the North Middlesex Hospital, came under the care of one of us (D. G. F.) in January 1947. She has been under continuous observation from early 1940, and it has been possible to abstract extensive records of her case from that time. Her illness dates from October 1938. The presenting feature was anaemia, which was accentuated in cold weather and was sometimes accompanied by slight jaundice. This anaemia necessitated her admission to hospital for long periods every winter from 1939–40 to 1942–3, but has not done so since. In the cold weather her hands, feet, nose, and ears go blue or white, and feel numb; gangrene has not occurred. On particularly cold days she has observed reddening of the urine; shivering and general aching have occurred on cold days, but not headache, nor has she had fever so far as is known. The spleen has usually been just palpable, and on one occasion (at a time when the haemoglobin was at its lowest recorded level of 4·4 gm. per 100 ml.) its lower pole was palpable one inch below the costal margin. The liver edge at this time was palpable midway between the costal margin and the umbilicus; it was enlarged two fingers' breadth below the costal margin on another occasion when the haemoglobin was as low as 6·5 gm. per 100 ml., but has been found in the normal position at all other times. The lymph-nodes have not been enlarged. Since 1947 she has twice had thrombophlebitis of the veins of the leg; small leg ulcers appeared on one of these occasions, and once spontaneously. The skin texture has been normal, without signs of scleroderma.

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Neither bile-salts nor bile-pigments have been found in the urine. X-rays, taken on account of pain in the neck, revealed osteoarthritis of the cervical spine. Otherwise physical examination has revealed no abnormality. She has had no other serious illnesses or operations except right inguinal herniotomy in 1942. She cannot recall symptoms suggestive of upper or lower respiratory disease in the six months prior to the onset of her illness. She has had three children and three miscarriages; one miscarriage occurred after the first child, and the other two between the second and third children. The children (two sons and a daughter) have been examined. They presented neither anaemia, jaundice, nor splenic enlargement. The osmotic fragility of the red cells in all three was normal, and cold agglutinins were not present in their sera at significantly raised titres. The patient's father and mother did not suffer from anaemia, jaundice, or gall-stones; the father died of an 'epileptic fit' and the mother from 'oedema'. The patient received two courses of neoarsphenamine and one of autohaemotherapy without apparent benefit. She has recently been given 5 mg. o adrenocorticotrophic hormone six-hourly for one week, without any change in the agglutinin or haemolysin titres, the haemoglobin level, or the reticulocyte count. She has, so far as possible, lived in warm rooms, dressed warmly, and avoided exposure to cold. She has taken iron salts by mouth for a number of years. She has kept comparatively well for some years, and this may well be due to the care she has taken of herself. Her employment as a cook has probably helped. Splenectomy was suggested but declined.

Clinical investigation

Raynaud's phenomena. On immersion of an arm in water at 12° C. the skin became a mottled blue and white, and some discomfort was experienced. At 4° C. the skin rapidly became white, and pain was soon intolerable. Mr. J. H. Dobree, consultant in ophthalmology, used a slit-lamp to investigate the effects of cooling the conjunctiva; the changes were clear-cut and striking. The red cells collected into clumps, with stretches of clear plasma intervening. At first the columns of cells and plasma moved slowly along the capillaries, but with further cooling complete arrest occurred; at this stage a peculiar coiled-spring-like movement of the capillaries was observed. On warming, the flow was resumed, at first spasmodically, the cells remaining clumped; then, quite abruptly, the clumps dispersed and continuous flow was restored. It was found easier to cool by holding a smooth piece of ice to the anaesthetized conjunctiva than by irrigating with ice-cold saline. The changes could be followed with a good hand-lens, though they might have been missed by someone who had not previously seen the phenomena under the slit-lamp.

Evidence of intravascular haemolysis. Haemolysis *in vivo* was demonstrable by the Rosenbach test. The patient's right arm was immersed in water at 12° C. for 20 minutes. Venous return was not obstructed, and the patient was instructed to avoid muscular movement. At the end of this time blood was withdrawn simultaneously from the antecubital veins of both forearms, and serum allowed to separate from both specimens at room temperature. The serum from the right arm was cherry-red in colour, while that from the left was normal. Haemoglobin was demonstrated spectroscopically in the former specimen, but not in the latter; the amount of haemoglobin was estimated at 50 mg. per 100 ml., by converting it to alkaline haematin and comparing the serum in a Spekker absorptiometer with graded dilutions of a serum containing known amounts of the same substance. Oxyhaemoglobin has been demonstrated spectroscopically on two occasions in samples of red urine; no significant excess of red cells was seen in the centrifuged specimens on either occasion.

Laboratory investigations

Haematology. Her haemoglobin and red-cell levels have been estimated on many occasions, and tend to fall in cold and rise in warm weather. They were at their lowest in the winter of 1940, being 4·4 gm. per 100 ml. and 1,500,000 per c.mm. respectively. The highest haemoglobin levels have been 11·8 and 12·4 gm. per 100 ml., both after rest in bed and iron by mouth for some weeks in hospital without transfusion. The reticulocyte percentage has varied between 1 and 14. Increased anisocytosis and polychromasia have generally been present. The mean corpuscular volume was estimated on two occasions, and found to be 120 and 107 c. μ, the corresponding haemoglobin levels being 4·4 and 10·4 gm. per 100 ml. respectively. On the former occasion five normoblasts per 100 nucleated cells were observed; they have not been seen on any other occasion. The total and differential white-cell counts have always been within normal limits. Serum-bilirubin has been estimated on several occasions, and has varied between 0·2 mg. per 100 ml. (haemoglobin 11·1 gm. per 100 ml.) and 4·0 mg. per 100 ml. (haemoglobin 4·4 gm. per 100 ml.). Schumm's test was positive. The serum-proteins have twice been found normal: total 6·5 gm. per 100 ml., albumin 4·4 gm., globulin 2·1 gm. (1941), and total 6·9 gm. per 100 ml., albumin 4·8 gm., globulin 2·1 gm. (1949).

Serology. The patient's blood group is B, Rh-negative. The Wassermann and Kahn reactions have been negative on four occasions. Her serum contains a cold agglutinin which agglutinates her own corpuscles and those of normal group O and B subjects to a consistently high titre (64,000 at 2° to 5° C.). The activity of the agglutinin sharply diminishes with a rise in temperature, but is still considerable (titre 256) at 20° C. Its upper thermal limit is 29° C. Before investigation by one of us (J. V. D.), the Donath-Landsteiner test had been reported negative on three occasions, but it is known that on two of these occasions the report was given with some hesitation. One of us (J. V. D.) has, however, detected and titrated a cold haemolysin in five samples of her serum (for methods see Dacie, 1950*a*, *c*). Haemolysis took place on warming after cooling, without acidification of the serum, though it was increased by adjustment of the pH of the cell-serum suspension to within or below the physiological range, that is within the pH range 7·4 to 6·6. The Donath-Landsteiner reaction, even as normally performed without acidification, must therefore be reported by us as positive in this patient. The haemolysin titre was 2,048 at the optimum pH. The lysin is thermostable; it was not destroyed by heating to 56° C. for 30 minutes. Its action is not entirely dependent upon the presence of complement in the cold phase, but it is enhanced by it; complement is essential in the warm phase. The Coombs test was found to be positive in 1948. This test has been repeated more recently, and it was found that the patient's corpuscles, even if separated from serum at 37° C., were agglutinated by anti-globulin rabbit serum after repeated washings in warm saline, thus confirming the previous report. This 'incomplete' antibody is considered to be an incomplete cold antibody (Dacie, 1950*b*) irreversibly adsorbed as the result of chilling *in vivo*. The fact that an incomplete form of cold antibody is being formed, in addition to the cold agglutinin and haemolysin, has been confirmed by subjecting normal corpuscles to the action of anti-globulin rabbit serum, after sensitizing them in the cold in the patient's serum and then repeatedly washing them with warm saline so as to elute the cold agglutinin. Such cells gave strongly positive Coombs tests; the highest observed titre of incomplete antibody was 4,096.

Summary. This woman presented Raynaud's phenomena, a chronic haemolytic anaemia, and cold haemoglobinuria. A cold agglutinin, a cold haemolysin,

and an incomplete cold antibody were present in her serum at high titres. Thrombosis of superficial veins has occurred on two occasions.

Case 2

A man aged 78 years came under the care of one of us (K. D. K.) in February 1948. His symptoms started one month before his first attendance, and continued until his death on Christmas Eve, 1949. He complained of pain and cyanosis of the hands, and of coldness of the feet in the cold weather, or on immersion in cold water. He never noticed reddening of his urine. In December 1949 he complained for the first time of cramps in his fingers, and pain in his legs (intermittent claudication). He was pale and slightly icteric. In cold weather his fingers and face became blue. Subungual splinter haemorrhages were a feature. The liver and spleen were not palpably enlarged. His chest was emphysematous, and his blood-pressure 180/90. The peripheral pulses were all palpable with the exception of that in the right dorsalis pedis artery. Examination revealed no other abnormality. He was given transfusions for anaemia in February 1948 and February 1949, and iron salts by mouth repeatedly. He kept in the warm as much as possible, and dressed warmly in cold weather with some benefit. He was not considered a suitable subject for splenectomy. He developed pneumonia in December 1949, went into coma, and died after an illness lasting two or three days. A post-mortem examination was performed several days later.

Clinical investigations

Raynaud's phenomena. Pressure on blue skin did not produce blanching, which is contrary to the usual finding in a case of Raynaud's syndrome. The observation is consistent with clumping and stasis of red cells in the capillaries. On cooling the conjunctiva, clumping of red cells with stretches of intervening clear plasma, and cessation of blood-flow were readily seen with a hand-lens.

Evidence of intravascular haemolysis. Both legs and an arm were cooled in water at 16° C. for half an hour. Serum from the cooled arm was tinged with red, and haemoglobin was demonstrated spectroscopically in this serum and in the urine passed afterwards. Haemoglobinuria was not visible to the naked eye.

Laboratory investigations

Haematology. The haemoglobin and red cells were estimated on a number of occasions, and tended to increase in the summer and decrease in the winter. The haemoglobin levels varied between 6·7 and 11·6 gm. per 100 ml., and the red cells between 1,860,000 and 3,380,000 per c.mm. The reticulocyte percentage ranged from 10 to 20, and the mean corpuscular volume from 70 to 115 c.μ. Several total and differential white-cell counts were within normal limits. The serum-bilirubin varied between 1·6 and 6·3 mg. per 100 ml. The excretion of faecal urobilinogen for one 24-hour period was 1,200 mg. Osmotic fragility was normal. The serum-proteins were 7·1 gm. per 100 ml. (albumin 4·8 gm., globulin 2·3 gm.). The clotting time (Lee and White) was 6 minutes, and bleeding time 1 minute. The prothrombin time was twice found to be normal.

Serology. The patient's cells were of blood group O. The Wassermann and Kahn reactions were negative. A Donath-Landsteiner test performed without acidification was negative. The following investigations were carried out by one

of us (J. V. D.) who found that the patient's serum contained an agglutinin which agglutinated his own cells and normal group O cells to a titre of 128,000 at 2° to 5° C. The upper thermal limit of the agglutinin was 31° C. A cold haemolysin was detected with characteristics somewhat similar to, but not identical with, those found in Case 1. Acidification of the serum was necessary for haemolysis to take place. The titre at optimum pH was 1,024. The upper thermal limit for adsorption of the haemolysin was 25° to 30° C. The haemolysin was thermostable, but, unlike that of Case 1, needed complement in both the cold and warm phases of the reaction. The direct and indirect Coombs tests were positive, as in Case 1.

Miscellaneous investigations. An X-ray of the chest was normal. A fractional test meal was normal. The serum alkaline phosphatase was 10 King-Armstrong units.

Post-mortem examination

General appearances. The body was that of an elderly man in a moderate state of nutrition. It presented a moderate degree of generalized icterus.

Respiratory system. Bronchopneumonia was found affecting the lower lobe of the left lung.

Cardiovascular system. Heart. The most striking feature was the presence of a fibrinous papilliform vegetation, about 7 mm. in diameter, attached to an atheromatous ulcer on the left anterior cusp of the aortic valve. *Coronary vessels.* Patchy subintimal atheroma was observed; the right coronary artery was occluded by a recent thrombus 2 cm. from its origin. *Peripheral vessels.* The arteries of the right lower limb were dissected; a recent thrombus was found in the femoral artery at its junction with the external iliac artery, and an older thrombus was present in the upper part of the popliteal artery. A dorsalis pedis artery could not be identified.

Abdominal viscera. Liver. The organ weighed 2,000 gm.; an obvious excess of fat was present. *Spleen.* No obvious macroscopic abnormality could be seen except an increase in size to about twice the normal. *Other viscera.* No macroscopic abnormalities were observed.

Bone-marrow. The sternum was examined; the marrow was deep red in colour.

Histology

Aortic valve. Evidence of early organization at the base of the vegetation was found.

Right femoral artery. The lumen was almost occluded by a recent thrombus, which was adherent to the intima over a large part of its circumference.

Popliteal artery. The lumen was almost completely occluded by an organized thrombus.

Posterior tibial artery. Mönckeberg's medial sclerosis was present.

Lower lobe of left lung. The alveoli and smaller bronchioles contained a purulent exudate. The larger bronchioles were unaffected.

Liver. Signs of mild venous congestion, with degeneration of the central cells of the lobules, were present. In addition there was a slight increase of fibrous tissue in the portal tracts, and a little lymphocytic infiltration. Free iron was present in the parenchymal and Kupffer cells.

Spleen. The histological appearances were spoilt by post-mortem autolysis.

Kidney. The glomeruli were normal. There was a striking increase of iron in the renal tubules, particularly in the second convoluted and collecting tubules.

Bone-marrow. The histological changes in the sternal marrow were obscured by post-mortem autolytic changes.

Summary. This man presented Raynaud's phenomena and a chronic haemolytic anaemia. Haemoglobinuria was minimal. Haemoglobinaemia and haemoglobinuria could be detected spectroscopically after experimental cooling of the limbs. Haemoglobinuria was not detected at other times during his stay in hospital. The patient himself was not aware of the passage of dark urine at any time. The striking haemosiderosis of the renal tubules suggests nevertheless that minor degrees of haemoglobinuria must have occurred from time to time. A cold agglutinin, a cold haemolysin, and an incomplete cold antibody were present in his serum at high titres. Multiple arterial thromboses appeared in the terminal phase of his illness.

Case 3

A married woman, aged 67 years, was referred to one of us (J. M. F.) in November 1948, and has attended at intervals since. Her illness started in the winter of 1947 when her hands, nose, and ears, but not her feet, became white and numb in cold weather. Lately, instead of going white, the hands have become red, then blue and painful. A small patch of gangrene appeared on the right thumb in January 1949. A constant slight cyanotic mottling of her hands has been present throughout the period of observation, even in warm weather. Since the attack of gangrene, the thumb has in addition been persistently dark grey in colour, and the patient has complained of its feeling numb. Early in the winter of 1948 she began to feel tired, and was observed to be clinically anaemic. This anaemia disappeared during the summer of 1949, but reappeared in the winter. Jaundice has not been observed. On particularly cold days she has passed very dark urine. The liver, spleen, and lymph-nodes have not been clinically enlarged. The blood-pressure has been in the neighbourhood of 200/120, and the heart has been slightly enlarged. No other abnormalities have been detected. She had a cholecystectomy for gall-stones in 1931, but has had no other serious illnesses, accidents, or operations. She has two sisters aged 73 and 75 years, and two children aged 33 and 36 years. One sister had anaemia 'in her teens', and both children had jaundice simultaneously when aged 10 and 13 years respectively. There is no other family history of anaemia, jaundice, gall-stones, or Raynaud's phenomena. She has dressed warmly, and kept in the warm as much as possible during cold weather, with benefit. She has been given iron repeatedly by mouth since November 1948.

Clinical investigations

Raynaud's phenomena. On immersion of one hand and forearm in water at 15° C. slight blanching, but no other change, was noted, and there was no pain. It was not considered justifiable to make any more rigorous tests in view of her previous gangrene. Changes precisely similar to those in the other two cases were readily seen with a hand-lens on cooling the conjunctiva.

Evidence of intravascular haemolysis. The left forearm and hand were placed in water at 15° C. for 10 minutes. Serum obtained from blood taken from the chilled arm was tinged with red. The patient brought a specimen of urine passed on a cold day. It was plum-coloured. Spectroscopy confirmed the presence of oxyhaemoglobin; microscopic examination at the same time showed no excess of red blood-cells in the centrifuged deposit.

Laboratory investigations

Haematology. Her haemoglobin level and red-cell count were at their lowest when she was first seen in November 1948, being 7·4 gm. per 100 ml. and 3,300,000 per c.mm. respectively. During the summer months of 1949 a haemoglobin level of 14·8 gm. per 100 ml. and a red-cell count of 5,000,000 per c.mm. were reached. In the winter the haemoglobin level fell once more to 11·4 gm. per 100 ml. and the red-cell count to 3,300,000 per c.mm. The reticulocyte percentage has ranged between 0·6 and 6·0. The mean corpuscular volume has varied between 80 and 108 c.μ. The total and differential white-cell count was normal on several occasions. The serum-bilirubin has varied between 0·3 and 1·8 mg. per 100 ml. The serum-proteins on one occasion were 6·8 gm. per 100 ml. (albumin 4·3 gm., globulin 2·5 gm.) and on another 6·9 gm. per 100 ml. (albumin 4·8 gm., globulin 2·1 gm.).

Serology. The patient's red cells were of blood group O. The Wassermann and Kahn tests were negative. The following investigations were made by one of us (J. V. D.). Her serum contained a cold agglutinin which agglutinated her own corpuscles and those of normal group O subjects to a consistently high titre (64,000 at 2° to 5° C.). The agglutinin was still markedly active at 20° C., and its upper thermal limit was 31° C. A cold haemolysin was detected having characteristics identical with those found in Case 2.[2] Haemolysis occurred on warming after cooling, after acidification of the serum to the pH range 7·4 to 6·6 (physiological level or below), but not otherwise. The haemolysin titre was 2,048 at the optimum pH. The haemolysin was thermostable, not being destroyed by heating to 56° C. for 30 minutes. Complement was necessary both in the cold and warm phases. The direct and indirect Coombs tests were positive, as in the other two cases; the highest observed titre of incomplete cold antibody was 320.

Summary. This woman presented Raynaud's phenomena, a haemolytic anaemia, and cold haemoglobinuria. A cold agglutinin, a cold haemolysin, and an incomplete cold antibody were present in her serum at high titres. The persistence of changes in the thumb after the resolution of gangrene suggests that the gangrene was caused by an arterial thrombosis.

Comment

The patients whose histories are given above have several features in common. The most remarkable pathological finding is the presence in their sera of cold auto-antibodies at very high titres. Raynaud's phenomena and a chronic haemolytic anaemia, made worse by cold, have been present in all three patients, and in each case intravascular haemolysis resulting in local haemoglobinaemia has been provoked by experimental cooling of a limb. Haemoglobinuria after exposure to cold undoubtedly occurred in two patients; its occurrence can be presumed with some probability in the third. The aetiology in all three instances is unknown; there was no clinical or serological evidence of syphilis. Certain minor differences have been noted between the behaviour *in vitro* of the haemolysins present in the sera of these patients (see Table I). The antibody in Case 1 differs from that of the other two cases in respect of the effect of pH and of its requirement of complement in the cold phase of the haemolytic reaction.

[2] A more detailed study of the haemolysin from Case 3 is given by Dacie (1950c).

We do not wish to overemphasize the importance of these variations in behaviour *in vitro*, for work in progress suggests that the differences are essentially quantitative, and that the mechanism of haemolysis is essentially the same in each. For this reason, and because of the very close clinical similarity between the patients, we believe it justifiable to bring them together into a single clinical group.

TABLE I

Characteristics of the Cold Antibodies in the Sera of Cases 1, 2, and 3

Patient	Cold agglutinin titre		Upper thermal limit for adsorption of agglutinin	Cold haemolysin titre		Effect of pH on haemolysis	Upper thermal limit for adsorption of haemolysin	Necessity for presence of fresh serum in cold phase o haemolysis
	20° C.	2–5° C.		at pH 7·2–7·5	at optimum pH			
Case 1								
28.10.49	256	64,000	29° C.	256	2,048	Less marked; some haemolysis in unacidified serum	30° C.	Not necessary, but enhances haemolysis
Case 2								
16.12.49	1,024	128,000	31° C.	128 (traces of haemolysis)	1,024	Marked; no haemolysis in unacidified serum	25°–30° C.	Necessary
Case 3								
26.4.49	128 (19° C.)	64,000	30° C.	..	512	Marked; no haemolysis in unacidified serum	30° C.	Necessary
13.6.49	16 (22° C.)	32,000	..	..	..	,, ,,	..	,,
11.10.49	..	32,000	..	..	..	,, ,,	25°–30° C.	,,
6.3.50	1,024	64,000	31° C.	64 (traces of haemolysis only)	2,048	,, ,,	25°–30° C.	,,

Discussion. Cases Recorded in the Literature

The syndrome under discussion has been observed in a number of diseases, in acute and chronic forms (Stats and Wasserman, 1943, and see under *Aetiology*). The present paper is concerned only with chronic examples of unknown aetiology. Nine adequately documented cases have been found. Outstanding features of these and of our own cases are shown in Tables II and III. A number of cases have been rejected for reasons given later.

Age and sex incidence. Seven of the 12 patients were men, and five women. They were all in later age-groups, only one being under 50 years. The disease appears therefore to be one of later life and to affect the sexes equally, but the series is small, and any definite conclusions would be unjustified (Table II). The disease has been recorded in persons of European and of African descent. It is believed to be non-familial and acquired.

Raynaud's phenomena. These were present in all 12 cases. Gangrene occurred in four (McCombs and McElroy, 1937; Benians and Feasby, 1941, second case; Stats and Bullowa, 1943; our Case 3).

Evidence of intravascular haemolysis. Haemoglobinaemia has been observed in blood withdrawn from an experimentally cooled extremity (Ernstene and

Gardner, 1935; Stats and Bullowa, 1943; Malley and Hickey, 1949; our three cases), but only doubtfully in the general circulation, presumably owing to dilution (Roth, 1935). Stats and Bullowa found 500 mg. haemoglobin per 100 ml. in blood from the cooled arm; Malley and Hickey found 373 mg. per 100 ml. The figure in our first case was 50 mg. per 100 ml. Haemoglobinuria[3] has been recorded in nine cases (Table II). It occurred paroxysmally, and only in really cold weather. It has been produced experimentally by cooling of limbs in five of these cases (Roth, 1935; Salén, 1935; Whittle, Lyell, and Gatman, 1947; Malley and Hickey, 1949; and our second case, though in the latter it was only demonstrable spectroscopically). Several limbs need to be cooled simultaneously before haemoglobinuria can occur.

Haematology. Anaemia of varying degree was present in 10 of these cases. Significant anaemia was absent in two (Roth, 1935; Stats and Bullowa, 1943). Direct or indirect evidence of a haemolytic process was found in the whole series (Tables II and III). Haemolysis was apparently going on continuously in some of these patients, as anaemia was always present. Schumm's test for methaemalbuminaemia has been found positive in two cases (Malley and Hickey, 1949, and our first case).

Serology. Wassermann and similar tests were made in 11 of these cases and repeatedly found to be negative. Cold agglutinins at high titres have been constantly present, the recorded values ranging from 1,024 to the scarcely credible figure of 2,000,000. An excellent review of the occurrence and significance of these agglutinins is to be found in the paper by Stats and Wasserman (1943). Cold haemolysins were found in all three of our cases at titres ranging from 512 to 2,048 at optimum pH. The Donath-Landsteiner test with unacidified serum was positive in Case 1; it was positive in our other two cases only with serum previously acidified to the physiological range or below. The test has been recorded as positive with unacidified serum in three cases from the literature: it was positive on four occasions prior to an operation in Ernstene and Gardner's case (1935) and negative on 17 subsequent occasions; it was doubtfully or weakly positive in the cases reported by Roth (1935) and Salén (1935). The test (using unacidified serum) was negative in four other cases from the literature. Complement was needed in the cold phase as well as in the warm phase in Cases 2 and 3 of our series; it was not essential in the cold phase in Case 1, though its presence enhanced haemolysis. The significance of these findings is discussed in the commentary on our own cases, and in the section dealing with the mechanism of haemolysis. The direct Coombs test was positive in all three of our cases, and in the only other case in which it was undertaken (Malley and Hickey, 1949).

Pathology. Two autopsies have been reported. In Malley and Hickey's (1949) case the spleen was enlarged and avascular. The pulp contained much interstitial hyaline material, consisting in part of closely packed circular bodies,

[3] The diagnosis of haemoglobinuria rests upon the results of spectroscopic and microscopic examination of the urine in six cases, upon the results of chemical tests and microscopic examination in a seventh, and upon clinical evidence only in the remaining two.

TABLE II

Cases of Raynaud's Disease, Chronic Haemolytic Anaemia, and the Formation of Cold Auto-antibodies: General Data

Authors	*Sex*	*Age (years)*	*Duration (years)*	*Cold agglutinin titre*	*Anaemia*	*Haemoglobinuria*	*Raynaud's phenomena*	*Haemolysis on experimental cooling of limb(s)*	*Haemoglobinuria on experimental cooling of limb(s)*	*Clumping of red cells on cooling*	*Wassermann reaction*	*Donath-Landsteiner test (unacidified serum)*
Roth (1935)	M	59	2	Cold agglutinins present	No	Yes	Yes	Yes	Yes	..	Negative	1 positive, 1 negative
Salén (1935)	M	50	4	1,024	Yes	Yes	Yes	..	Yes	..	Negative	Weakly positive
Ernstene and Gardner (1935)	M	38	2	1,280	Yes	Yes	Yes	Yes	Yes	..	Negative	4 positive, 17 negative
McCombs and McElroy (1937)	M	57	3	1,024	Yes	Yes	Yes	..	..	..	Negative	Negative
Benians and Feasby (1941, 2nd case)	F	65	3	4,000	Yes	No	Yes	..	..	..	Negative	..
Stats and Bullowa (1943)	M	64	15	32,000	Hb. 84 %	Yes	Yes	Yes	..	Yes	Negative	Negative
Stratton (1943)	F	62	..	256 (room temperature)	Yes	..	Yes	..	..	..	..	..
Whittle, Lyell, and Gatman (1947)	F	56	5	2,000,000	Yes	Yes	Yes	..	Yes	Yes	Negative	Negative
Malley and Hickey (1949)	M	69	4	4,096	Yes	Yes	Yes	Yes	Yes	..	Negative	Negative
Our Case 1	F	60	11	64,000	Yes	Yes	Yes	Yes	..	Yes	Negative	Positive
Our Case 2	M	78	2	128,000	Yes	Probable	Yes	Yes	Yes	Yes	Negative	Negative
Our Case 3	F	67	1	64,000	Yes	Yes	Yes	Yes	..	Yes	Negative	Negative

Table III

Cases of Raynaud's Disease, Chronic Haemolytic Anaemia, and the Formation of Cold Auto-antibodies: Evidence Pointing to a Haemolytic Origin of the Anaemia

Authors	*Haemoglobin (% or gm./100 ml.)*	*Red cells (millions per c.mm.)*	*Mean corpuscular diameter (μ) or volume (c.μ)*	*Reticulocytes (%)*	*Jaundice*	*Serum-bilirubin/100 ml., icterus index, or faecal urobilinogen/24 hrs.*	*Splenic enlargement*	*Osmotic fragility (% NaCl)*	*Production of haemolysis by experimental cooling of limb(s)*
Roth (1935)	14·5 gm	..	..	..	..	..	0	..	Yes
Salén (1935)	52 %	2·90	Normal	..	..	Van den Bergh reaction: indirect positive. Icterus index 12	0	0·42–0·24	..
Ernstene and Gardner (1935)	10·5 gm.	3·80	..	..	..	..	0	0·4 –0·34	Yes
McCombs and McElroy (1937)	10·5–11·5 gm.	3·12	..	1·6	..	Icterus index 5	0	0·46–0·32	..
Benians and Feasby (1941, 2nd case)	52 %	..	M.C.D. 7·4 μ	..	Yes	..	+	Normal	..
Stats and Bullowa (1943)	84 %	..	M.C.D. 7·3 μ	1·5	..	Icterus index under 3. Faecal urobilinogen 70 mg.	..	0·44–0·32	Yes
Stratton (1943)	52 %	2·50	..	29·0	Yes	Serum-bilirubin 12·5 units	..	Increased	..
Whittle, Lyell, and Gatman (1947)	'Anaemic'	..	Macrocytosis	5	Yes	Van den Bergh reaction: indirect positive. Serum-bilirubin 1·8 mg.	0	Normal	..
Malley and Hickey (1949)	55–85 %	2·91–3·72	M.C.D. 8·56 μ	2–12	Yes	Serum-bilirubin 3·6–5·78 mg.	0	0·44–0·28	Yes
Our Case 1	4·4–12·4 gm.	1·50–4·40	120 and 107 c.μ	1–14	Yes	Serum-bilirubin (with Hb. 4·4 gm. per 100 ml.) 4 mg.; at other times 0·2–1 mg.	+	0·5 –0·4	Yes
Our Case 2	6·7–11·6 gm.	1·86–3·38	70–115 c.μ	10–20	Yes	Serum-bilirubin 1·65–6·3 mg. Faecal urobilinogen 1,200 mg.	0	0·48–0·36	Yes
Our Case 3	7·4–14·8 gm.	3·30–5·00	80–108 c.μ	0·6–6	No	Serum-bilirubin 0·3–1·8 mg.	0	..	Yes

and in part of homogeneous eosinophilic material. This appearance was considered to represent haemolysed red cells in different stages of disintegration. The liver was not cirrhotic, and gall-stones were not present. Sections of the bone-marrow showed normoblastic hyperplasia. Much pigment, some containing iron, was found in the spleen, liver, kidney, and other organs. Thrombi were present in the spleen and elsewhere. The findings in our Case 2 are reported above.

Rejected cases. A number of cases had claims for inclusion in the present series, but have been rejected for the reasons given after the names of the authors who reported them. Boxwell and Bigger (1931), and Davidson (1932): these two cases may represent incomplete forms of the syndrome, but Raynaud's phenomena and haemoglobinuria were absent. Debenedetti (1929) and Köpplin (1936): see page 288 (relationship to congenital acholuric jaundice). Aubertin, Foulon, and Bretey (1929): the relationship of the agglutinin to cold was not stated; there was a bleeding tendency, and a possibility of cirrhosis of the liver. Sézary, Kipfer, and Gharib (1938): the cold agglutinin was thermolabile, and there was possibly cirrhosis of the liver. Watson (1939): the condition was possibly secondary to an ovarian cyst. Reisner and Kalkstein (1942): cold agglutination was irreversible, and there was a bleeding tendency. Benhamou, Zermati, and Assus (1948, Case 1): it is impossible to exclude malaria as cause. Baumgartner (1948): the condition was possibly secondary to virus pneumonia. Mellinkoff and Pisciotta (1949): the history was short. Guthrie and Huck (1923), Iwai and Mei-Sai (1925), Masters, Zerfas, and Mettel (1929), Lloyd and Chandra (1930), LeGoff (1933), Higgins and Roen (1943), and Gördüren (1946) give inadequate accounts.

Mechanism of Raynaud's phenomena. A reasonably conclusive case can be made for the theory that cold agglutinins are responsible for the Raynaud's phenomena by causing a clumping of red cells in skin capillaries, and so bringing about a cessation of blood-flow. The phenomena have been observed in other diseases in which cold agglutinins have been found: for example, in leukaemia (Alexander and Thompson, 1925; Gautier, Heimann, and Laudat, 1939), congenital acholuric jaundice (Köpplin, 1936), probable atypical pneumonia (Helwig and Freis, 1943; Forbes, 1947; and Baumgartner, 1948), malaria (Benhamou, Zermati, and Assus, 1948), and in three cases of unknown or uncertain aetiology (Iwai and Mei-Sai, 1925; Gördüren, 1946; Mellinkoff and Pisciotta, 1949). Gangrene occurred in Köpplin's case. Direct evidence has been obtained of this clumping and arrest of blood-flow by observation of the cooled conjunctiva and skin through slit-lamp and skin capillary microscopes. Observations of the conjunctiva were made by Iwai and Mei-Sai (1925), Stats and Bullowa (1943), Gördüren (1946, two cases), and ourselves (three cases). Skin observations were made by Whittle, Lyell, and Gatman (1947), Benhamou, Zermati, and Assus (1948), and Baumgartner (1948). Iwai and Mei-Sai suggested that the cessation of blood-flow was due to the increased viscosity of the agglutinated corpuscles, and supported their hypothesis by observations of the passage of blood from their patient through cooled capillary glass tubing.

Alternatively the obstruction to flow might be due to the hold-up of clumped cells at the bifurcations of larger vessels.

Mechanism of haemolysis. Part, at least, of the haemolysis occurring *in vivo* takes place in the circulating blood-stream, that is, is intravascular. Haemoglobinaemia has been observed in blood withdrawn from an experimentally cooled limb in six cases. Haemoglobinuria following exposure to cold has occurred clinically in nine of the reported cases, and has been reproduced experimentally by cooling of limbs in five. Schumm's test for methaemalbuminaemia (Fairley, 1940) has been positive in two cases. The role of cold in bringing about haemolysis *in vivo* is thus firmly based on repeated clinical and experimental observations. It is less certain, however, which type of antibody brings about the haemolysis. Previous attempts to demonstrate haemolysis *in vitro* have been largely unsuccessful, except by the application of artificial trauma to concentrated cell-suspensions agglutinated by chilling (Stats, 1945). It has been generally assumed until now that agglutinins, but not haemolysins, were present in the type of case under discussion (Stats and Wasserman, 1943; Stats, Wasserman, and Rosenthal, 1948). Stats and other workers found that cells tightly agglutinated by sera containing cold agglutinins in high titre were unusually sensitive to trauma (Stats, 1945; Whittle, Lyell, and Gatman, 1947; Malley and Hickey, 1949; Shen, Castle, and Fleming, 1944). Stats and his collaborators postulated that cold agglutinins were the responsible agents *in vivo*; that they caused damage to the red cells by powerful agglutination in skin capillaries exposed to low external temperature, and that the natural buffeting of the circulation provided the necessary element of trauma. A difficulty in accepting this hypothesis has been that the incidence of haemolysis *in vivo* has not clearly paralleled the titre of cold agglutinins or the severity of Raynaud's phenomena. Thus anaemia was absent or negligible in the cases reported by Roth (1935) and Stats and Bullowa (1943), yet Raynaud's phenomena were marked. On the other hand, some earlier reports have hinted at the existence of cold haemolysins. Donath-Landsteiner reactions (using unacidified serum) were weakly positive in the case reported by Salén (1935), and irregularly present in those reported by Roth (1935) and Ernstene and Gardner (1935). Dacie (1950*c*) found that cold haemolysins were regularly associated with cold agglutinins when the latter were present at high titre, and could be demonstrated *in vitro* if the patients' sera were acidified to the physiological range, or below, before the suspension of corpuscles was added. This happened in our second and third cases; a haemolysin could also be demonstrated in Case 1, but her serum differed slightly from that of the other two patients in that acidification was less necessary. It may be added that in syphilitic cold haemoglobinuria haemolysis is readily observed *in vitro*. In this condition, in which low titres only of cold agglutinins have usually been observed, it seems certain that haemolysis is brought about by the cold haemolysin alone. We conclude that, although the cold agglutinins may play a part in causing haemolysis *in vivo*, it is likely that the haemolysins are also of importance. The significance of the 'incomplete' cold antibody remains a matter for speculation.

Relationship to other conditions

Syphilitic cold haemoglobinuria. This disorder can be separated from the present syndrome on clinical and serological grounds. Past or present clinical evidence of syphilitic infection may be found, and the Wassermann reaction is almost always positive. Patients with the syphilitic disorder often suffer from urticaria and angioneurotic oedema on exposure to cold; such lesions have not been recorded in any of the present series of cases, and the application of ice to the skin failed to produce them in two (Roth, 1935; Malley and Hickey, 1949). No significant clinical evidence of syphilis has been found in any of the present series of patients. Wassermann reactions have been carried out in all but two, and have invariably been found negative. Cold agglutinins at enhanced titre are said to be very uncommon in syphilitic cold haemoglobinuria (Stats and Wasserman, 1943) and this would seem to be an important point in distinguishing between the two syndromes. Siebens, Zinkham, and Wagley (1948), however, have recently described two patients with serological evidence of syphilis in whom cold agglutinins were present at titres of 160 and 320. These titres are far below those of the present series, but it is possible nevertheless that the suggested criterion of difference may not be an entirely reliable one. It is possible also that the mechanism of haemolysis in the two syndromes is not so dissimilar as has been thought (Stats and Wasserman, 1943). Positive Donath-Landsteiner reactions, without acidification, have been recorded in several of the present series of cases. Very little is known about the effect of acidification upon haemolysis when the test is carried out in syphilitic cases. The Donath-Landsteiner reaction is admittedly positive, without acidification, in the great majority of cases of syphilitic cold haemoglobinuria, but in a small proportion of syphilitic cases it is said to be negative (Höglund, 1927, quoted by Stats and Wasserman, 1943). It would be interesting to know whether a cold haemolysin could be demonstrated in such cases by acidification of serum. Further consideration of these cold haemolysins is beyond the scope of this article, but a discussion will be found in Dacie's (1950c) paper. The serological findings in the present series indicate that a positive Donath-Landsteiner reaction is not pathognomonic of syphilis.

Nocturnal haemoglobinuria. This disorder is quite distinct both clinically and serologically. In nocturnal haemoglobinuria the patient's corpuscles are at fault, and undergo haemolysis in acidified normal serum; the patient's serum is normal. Cold agglutinins at raised titres are not found. The acid haemolysis test of Ham has been applied to the cells in two cases of the present series and found negative (Stats and Bullowa, 1943; Malley and Hickey, 1949). Cooling is not necessary to demonstrate the haemolysis of cells by normal serum in nocturnal haemoglobinuria, so there can be no relationship between the normal 'haemolysin' responsible for haemolysis in nocturnal haemoglobinuria, and the haemolysin which was active in our patients, as might be suggested by the necessity for acidification in both groups.

Congenital acholuric jaundice. Köpplin (1936) described a family with this disease in which the serum of one member contained a cold agglutinin at high

titre. This patient exhibited Raynaud's phenomena and haemoglobinuria, as well as a haemolytic anaemia. He propounded the hypothesis that cold agglutinins had appeared in response to the products of long-continued haemolysis. Debenedetti (1929) described a similar family. These are the only occasions on which cold agglutinins have been reported in congenital acholuric jaundice, which is not an uncommon disease. On the other hand the 12 cases collected in the present review presented no evidence of familial involvement. The late age incidence is also against any connexion between the two disorders. It is felt that the two diseases are entirely separate.

Chronic acquired haemolytic anaemia. The aetiology of chronic acquired haemolytic anaemia and of the condition now under discussion is unknown. Both appear to be due to a disturbance of immunity mechanisms, and they might conceivably be related. At first sight they appear to be quite distinct on clinical and serological grounds. The antibodies present in chronic acquired haemolytic anaemia are essentially 'warm' ones. Cold agglutinins are frequently present as well (Dameshek and Schwartz, 1940; Young and Lawrence, 1946); but their titre is generally not greater than 1,024, and they do not give rise to Raynaud's phenomena. Anaemia is invariable, and is clinically unrelated to cold, and often more severe than in the cases under discussion. Haemoglobinuria is rare. Further work is necessary to define more exactly the relationship between the two groups of cases.

Aetiology

An interesting group of cases has been described in which a clinical picture more or less closely resembling that of the present series has been associated with, or has followed, some quite different disorder. Thus Raynaud's phenomena, a haemolytic anaemia with or without haemoglobinuria, and cold antibodies appeared in two cases of leukaemia (Alexander and Thompson, 1925; Gautier, Heimann, and Laudat, 1939), in a case of malaria (Benhamou, Zermati, and Assus, 1948), and in a case of congenital acholuric jaundice (Köpplin, 1936). The syndrome, in part only, has occurred in a case of cirrhosis of the liver (Benhamou, Zermati, and Assus, 1948), in congenital acholuric jaundice (Debenedetti, 1929)—cirrhosis of the liver also being present in this case—and in a woman with an ovarian cyst (Watson, 1939). More acute symptoms and signs have followed primary atypical pneumonia; an acute haemolytic anaemia (with or without haemoglobinuria) and cold antibodies have been reported by Antopol, Applebaum, and Goldman (1939), Dameshek (1943), Horstmann and Tatlock (1943), Finland, Petersen, Allen, Samper, and Barnes (1945), Ginsberg (1946), and Stats, Wasserman, and Rosenthal (1948)—22 cases in all. Raynaud's phenomena and cold antibodies have been reported by Helwig and Freis (1943), Forbes (1947), and Baumgartner (1948). It is possible that the cases cited above are secondary examples of the condition now under review. The aetiology of the present series is unknown. There is evidence that cold agglutinins are bound up in some way with immunity mechanisms. They have frequently been found at raised titres as a result of certain infections, notably trypanosomiasis,

primary atypical pneumonia (Stats and Wasserman, 1943) and possibly malaria (Benhamou, Zermati, and Assus, 1948). It is known that the rise and fall of the cold agglutinin titre in primary atypical pneumonia is similar to that of an immune antibody reaction (Turner, Nisnewitz, Jackson, and Berney, 1943; Commission on Acute Respiratory Diseases, 1944; Finland, Petersen, Allen, Samper, and Barnes, 1945). Cold agglutinins are found in the γ-globulin fraction of serum-proteins, and are present at low titres in many if not all normal people (Stats and Wasserman, 1943). The disease under discussion may be due to some obscure disturbance of these mechanisms, resulting in the appearance of 'normal' antibodies at greatly enhanced titres.

Treatment

Splenectomy has some theoretical justification in this disease. Cold agglutinins are antibodies (see under *Aetiology*) and are produced to some extent by the spleen. Splenectomy might therefore produce improvement by removing a site of antibody production, as well as by removing an organ which filters damaged cells from the circulation. The possible similarity in mechanism to chronic acquired haemolytic anaemia has already been noted, and splenectomy in the latter disease has sometimes been wholly or partly successful (Welch and Dameshek, 1950). It has not yet been tried in the condition under discussion, but the authors feel that its trial in suitable cases would be justified. Failing splenectomy, treatment resolves itself into management. The patients should live in warm rooms, especially in the winter, and should dress warmly on going out into the cold. A good deal of benefit can be expected from these measures. Adrenocorticotrophic hormone was tried in small doses for a short time in one of our cases without any apparent benefit.

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Summary

1. Three patients are described who had cold agglutinins, cold haemolysins, and incomplete cold antibodies in their sera at high titres, the origin of these changes being unknown. They suffered from Raynaud's phenomena and a chronic haemolytic anaemia, both being more severe in winter. They all probably had attacks of haemoglobinuria in cold weather. The condition had lasted for a considerable time in all three cases.

2. Nine similar cases from the literature are reviewed.

3. The Raynaud's phenomena are almost certainly due to obstruction of the peripheral circulation caused by auto-haemagglutination *in vivo*. The relative importance of the cold agglutinins and the cold haemolysins in causing haemolysis *in vivo* is less clear.

4. The patients under discussion are thought to form a fairly homogeneous group which can be separated from other types of haemolytic anaemia, and particularly from syphilitic cold haemoglobinuria, by distinctive clinical features and laboratory findings.

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THE HEREDITARY AND FAMILIAL ASPECTS OF TOXIC NODULAR GOITRE (SECONDARY THYROTOXICOSIS)[1]

By LAURENCE MARTIN and R. A. FISHER

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In a previous investigation of the hereditary and familial aspects of exophthalmic goitre and nodular goitre (Martin and Fisher, 1945) a factor of recessive inheritance was detected which favoured the development of exophthalmic goitre, but no hereditary influence could be found for nodular goitre. Bartels (1941), from a similar study made in Copenhagen, had also detected a recessive factor in the occurrence of exophthalmic goitre, but he had included an unknown number of cases of toxic adenoma (secondary thyrotoxicosis) among his propositi and their affected relatives. Bartels admitted this lack of homogeneity, but believed that the mode of inheritance was the same in Graves's disease as in those cases of toxic adenoma which were influenced by heredity. He had found among the female relatives of his mixed group of propositi a greater number of sisters and sisters of parents, and a probably greater number of mothers, affected either by Graves's disease or by simple goitre than in the general population of Copenhagen. He considered that if the increase had affected only mothers and sisters it might have been explained by exogenous or environmental influences, but because sisters of parents were also affected it seemed that hereditary factors must have determined the occurrence of both Graves's disease and simple goitre. The further fact that these two conditions occurred with equal frequency in each group of relatives pointed to the conclusion that both were phenotypic manifestations of the same gene. The mode of inheritance was considered to be one of simple 'monomeric' recessivity, with pronounced sex-limitation to women and a manifestation of 70 to 80 per cent., either as Graves's disease or as simple goitre which might later become secondarily thyrotoxic. Bartels recognized that simple goitre might also be due to exogenous and non-hereditary influences, and since such goitres might also become thyrotoxic it was necessary to regard cases of toxic adenoma as a mixed group. Thus toxic adenoma might either result from thyrotoxic change in a simple goitre which was due to the gene which could also cause Graves's disease—in which case inheritance would be the same as for Graves's disease—or it might result from thyrotoxic change in a non-hereditary simple goitre due to exogenous or environmental causes. These findings, in effect, offered a unitary explanation, based upon heredity, for

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the occurrence of Graves's disease and of some cases of simple goitre and subsequent secondary thyrotoxic goitre. We could not accept these views unreservedly, but were unable to comment upon them in our previous paper (Martin and Fisher, 1945), although we had found no evidence favouring hereditary influence in our mixed group of toxic and non-toxic nodular goitres. It seemed desirable, therefore, to test Bartels's assertions by examining a series consisting entirely of cases of toxic nodular goitre (secondary thyrotoxicosis), and to compare the results with our previous series of exophthalmic goitrous cases and with a series of non-goitrous controls.

Material

The pedigrees of 100 consecutive patients with toxic nodular goitre (93 women and seven men) were obtained, and information was recorded concerning goitrous relatives. The diagnosis of toxic nodular goitre in the propositi was based upon the presence of a frankly nodular goitre, undoubted clinical evidence of thyrotoxicosis, and histological evidence from the goitres of those (the vast majority) who were submitted to thyroidectomy. The control series consisted of 100 non-goitrous female hospital patients between the ages of 45 and 80 years, thus corresponding to the age-groups of the toxic nodular goitre propositi. The goitres reported in the relatives of the toxic nodular goitre propositi and of the controls were classified, as in our previous paper, as follows:

Known exophthalmic goitre	(Ex.G.)
Known toxic goitre	(T.G.)
Known simple goitre	(S.G.)
Goitre not known to be toxic, or presumed simple . . .	(G.)

It should be added that the designation toxic goitre (T.G.) includes all cases of secondary thyrotoxicosis, whether the toxic goitre had become nodular or not.

Results

Of the 100 patients with toxic nodular goitre 28 (25 women and three men) gave a positive family history of goitre, which affected 46 relatives. Of the 100 controls, 11 gave a family history of goitre affecting 12 relatives. The details are contained in Table I, which also includes for comparison similar details of the 90 cases of exophthalmic goitre described in our previous paper. When any factor of recessive inheritance is sought among the relatives of the 100 toxic nodular goitre propositi, it will be recalled that the evidence rests upon the proportion of siblings affected by toxic goitre being significantly greater than the proportion of parents similarly affected. Table II shows the proportions of parents and siblings of the 100 toxic nodular goitre propositi suffering from toxic goitre (T.G.), as opposed to other forms. In relation to the families of the 90 patients with exophthalmic goitre (Martin and Fisher, 1945) attention was called to the contrast afforded by finding 16 out of 160 siblings showing exophthalmic goitre, whereas only one parent among 180 was similarly affected. In the present series of 100 families based on toxic goitre the corresponding figures (Table II) are three siblings (0·58 per cent.) out of 514, and no parent.

This slight degree of disproportion is insufficient to demonstrate any evidence of recessive inheritance, and the series clearly differs materially from the previously reported series of exophthalmic goitre. There is, indeed, a rather striking excess of goitrous relatives of the patients with toxic nodular goitre compared

TABLE I

	Goitrous relatives of 100 patients with toxic nodular goitre					*Goitrous relatives of 100 non-goitrous controls*					*Goitrous relatives of 90 patients with exophthalmic goitre (Martin and Fisher, 1945)*				
	Ex.G.	*T.G.*	*S.G.*	*G.*	*Total*	*Ex.G.*	*T.G.*	*S.G.*	*G.*	*Total*	*Ex.G.*	*T.G.*	*S.G.*	*G.*	*Total*
Mothers	1	..	4	4	9	..	1	..	..	1	..	1	5	..	6
Fathers	..	..	..	..	0	..	..	..	..	0	..	..	..	..	0
Sisters	3	3	6	13	25	1	1	2	1	5	8	2	3	3	16
Brothers	1	..	..	2	3	..	..	..	..	0	8	..	..	..	8
Sons	..	..	..	..	0	..	..	..	..	0	..	..	..	..	0
Daughters	..	1	..	1	2	..	..	..	1	1	..	..	..	1	1
Aunts	1	..	..	1	2	..	1	..	..	1	1	..	..	4	5
Female cousins	..	..	4	..	4	..	1	..	1	2	..	..	..	..	0
Nieces	..	..	..	1	1	..	..	1	..	1	..	..	..	..	0
Maternal grandmother	..	..	..	..	0	..	..	1	..	1	..	..	..	..	0
Total	6	4	14	22	46	1	4	4	3	12	17	3	8	8	36

TABLE II

Parents and Siblings of 100 Toxic Nodular Goitre Propositi, showing the Proportion Suffering from Toxic Goitre

	Affected	*Unaffected*	*Total*
Male:			
Brothers	0	268	268
Fathers	0	100	100
Total	0	368	368
Female:			
Sisters	3	243	246
Mothers	0	100	100
Total	3	343	346
Total:			
Offspring	3	511	514
Parents	0	200	200
Total	3	711	714

with those of the non-goitrous controls. This excess would be expected even if all familial tendencies were non-genetic. There is no significant excess among the sisters (25 out of 246) as compared with the mothers (nine out of 100). It was the disproportion of the corresponding ratios on which we relied in inferring a recessive gene in the case of exophthalmic goitre. It must, of course, be admitted that in diagnosing the nature of a goitre in an unseen relative from the statements of a lay propositus there are obvious sources of error, particularly because some cases of toxic goitre show exophthalmos. But in making our decisions between exophthalmic goitre and toxic goitre we took into account all distinguishing features such as the size, appearance, and duration of the goitre,

the age of the relative, and the presence of cardiac symptoms. Even if all the relatives described in Table I as having exophthalmic goitre (four siblings and one parent) had in fact suffered from toxic goitre, their addition to our analyses in Table II would not have altered the validity of our conclusions. It is also possible that the goitrous propositi were more aware of goitres in their relatives than the non-goitrous controls. This might affect the comparison we make with the relatives of non-goitrous controls, in which it should be noted that we draw no conclusion as to the hereditability of toxic nodular goitre. It would not attenuate the evidence, based on the contrast between the frequencies of affected mothers and sisters, which we regarded as significant in the case of exophthalmic goitres (Martin and Fisher, 1945).

Among the relatives of 100 non-goitrous patients, only one parent and one sibling were affected by toxic goitre (Table I). Out of 40 goitres (T.G., S.G., and G.) among relatives of the toxic nodular goitre propositi, there were only three toxic goitres affecting mothers (0) and sisters (3); among 11 similar goitres in the families of the controls, two toxic goitres affected a mother and a sister respectively. This comparison shows that, whatever may be the reason for the larger total number of goitres in the families of the toxic nodular goitre propositi, the special causes favouring the supervention of secondary toxic change show, in these data, no sign of difference between the two classes. It will be noticed that we have confined our analyses to relatives affected by toxic goitre, and have not included those affected by exophthalmic goitre or by simple goitre. We have thus dealt with pure material, and consider that if Bartels's (1941) views were correct we should have detected evidence of recessive inheritance, as we did in the case of exophthalmic goitre. We cannot positively assert from our present data that we have excluded any hereditary influence in the occurrence of toxic nodular goitre but, as was found with our mixed group of toxic and non-toxic nodular goitre cases (Martin and Fisher, 1945), we cannot detect evidence in favour of it. It must be admitted that many cases of simple goitre occur among the relatives of propositi having toxic nodular goitre, but this familial incidence does not require, although it does not exclude, hereditary influence.

Discussion

The practical outcome of the present investigation, in conjunction with our previous communication, is to add a new distinguishing feature in respect of heredity to the existing differences between exophthalmic goitre and toxic nodular goitre. Although a distinction between the two conditions is somewhat grudgingly made on grounds of clinical convenience, general opinion is still on the side of a common pathological basis for both. The same abnormal stimulus is believed to affect a previously normal thyroid to produce exophthalmic goitre (primary thyrotoxicosis), and to supervene upon a simple goitre to produce toxic goitre or toxic nodular goitre (secondary thyrotoxicosis). The clinical similarities are held to support the identity of the thyrotoxic process in both, but the differences are regarded as sufficient to warrant a distinction for the practical purposes of treatment. This is an illogical state of affairs, which arises

ultimately from our ignorance of the fundamental mechanism of thyrotoxicosis, and from misinterpretation of the histological appearances in the thyrotoxic thyroid gland. Because the thyroid epithelium is hyperplastic in both primary and secondary thyrotoxicosis, it has been assumed in the past that the causal thyrotoxic stimulus has been the same in both types. But this assumption may well be incorrect, for the thyroid epithelium may be hyperplastic in a variety of other circumstances, which include simple iodine deficiency, compensatory hyperplasia after partial thyroidectomy, and the administration of thiouracil drugs. It is not justifiable, therefore, to base conclusions as to the cause of epithelial hyperplasia of the thyroid upon histological examination, and we have no concrete evidence for assuming that the hyperplastic epithelium observed in primary and secondary thyrotoxicosis is produced by the same stimulus. The elucidation of the pathogenesis of primary and secondary thyrotoxicosis is more likely to be furthered by closer examination of their differences than by continued emphasis on their similarity. The demonstration of a hereditary influence in the development of primary thyrotoxicosis, and the lack of evidence for it in secondary thyrotoxicosis, certainly do not favour a common cause of both.

Summary

1. The familial occurrence of toxic nodular goitre (secondary thyrotoxicosis) has been investigated in 100 cases.

2. No decisive evidence of hereditary influence was obtained.

3. This finding is in contrast with the previous detection of a recessive factor favourable to the occurrence of exophthalmic goitre (primary thyrotoxicosis).

4. The identity of the thyrotoxic process in exophthalmic goitre and in toxic nodular goitre is questioned.

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THE OCCURRENCE OF HAEMOPHILIA IN THE HUMAN FEMALE[1]

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With Plates 30 and 31

HAEMOPHILIA is a disease of males, although its occurrence in females has always been theoretically possible. The bleeding tendency is inherited as a sex-linked recessive character, the transmission being through apparently unaffected

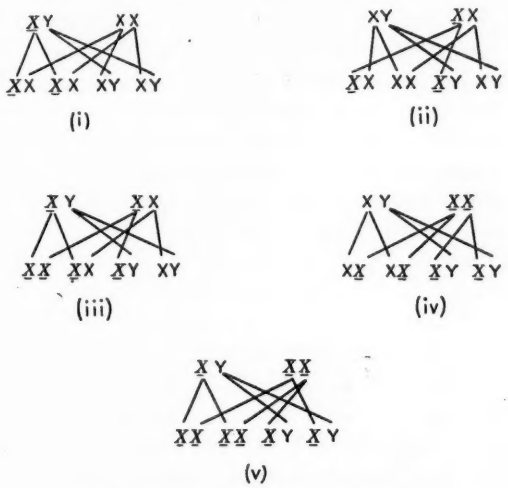

FIG. 1. Inheritance of haemophilia.

females. If X and Y represent the chromosomes which determine sex and $\underline{X}$ the chromosome which carries the recessive sex-linked character, the normal male would be represented by XY and the normal female by XX. In the inheritance of the disease there are two likely combinations and three further possible ones (Fig. 1). If the dominance of X over $\underline{X}$ is complete, only the haemophilic male ($\underline{X}$Y) and the homozygous female ($\underline{X}\underline{X}$) should have symptoms of the disease, the heterozygous female ($\underline{X}$X) being free of symptoms. As a rule the heterozygous female does not bleed more readily than the normal female. In some instances bleeding may be a little more profuse, but even in these it does not usually reach the severity of haemorrhage encountered in the

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affected male. It is as yet uncertain whether it may do so in individual instances, but a bleeding tendency of such severity in the heterozygous female would certainly be exceptional (Merskey and Macfarlane, 1951).

In order to establish the diagnosis of the homozygous haemophilic state in the female subject, it is necessary to show that her disease is clinically and pathologically indistinguishable from that which occurs in the male, and also that both her parents could have transmitted the affected gene (Fig. 1, iii); further, that all her sons are haemophilics and all her daughters are heterozygous or homozygous for haemophilia (Fig. 1, iv and v). Such a condition in a woman has not as yet been recognized beyond doubt (Andreassen, 1943; Wintrobe, 1946) although Gates (1946), in an extensive review, was prepared to accept the evidence as satisfactory in a number of cases. In an effort to explain the apparent absence of homozygous females it has been suggested that this combination of genes is lethal to the developing embryo. Brinkhous and Graham (1949) showed that in canine haemophilia it is possible to breed females who are homozygous, and there appears to be no reason why the human disease should not behave in the same way. A better explanation is the rarity of the mating required to produce such an individual. The union of a haemophilic man and a heterozygous haemophilic woman usually involves the marriage of cousins. Very few examples of such a marriage in haemophilic families have been recorded. A careful survey of the pedigrees in Bulloch and Fildes's (1911) monograph revealed 13 marriages between cousins, in two of which the husband was a bleeder, while the wife proved herself a carrier by bearing a bleeder son (Handley and Nussbrecher, 1935). One of these instances, occurring in the Mampel family (pedigree 389 in Bulloch and Fildes), must be discounted, since Klug (1926) has shown that the husband falsely alleged that he was a bleeder in order to escape military service. The second case was described by Wightman (1894; pedigree 431 in Bulloch and Fildes), the marriage producing two carrier daughters and one daughter who had no children, as well as an affected son. None of the daughters bled abnormally. Bulloch and Fildes (1911), after a full consideration of all the facts in their monograph, concluded that all statements alleging the occurrence of well-marked haemophilia in females were unsupported by adequate evidence. Snyder (1932), in a further analysis of the cases reviewed by Bulloch and Fildes, found 19 cases of alleged haemophilia in women. Fifteen of these women had normal fathers, and therefore could not be homozygous for haemophilia. The other four had haemophilic fathers, but each had at least one normal son, and therefore could not have been homozygous. In recent years a number of authors have described cases of alleged haemophilia in female subjects, but in none of these subjects have all the criteria of the homozygous haemophilic state been fulfilled. Warde (1923), Lloyd (1925), and Madlener (1928) described patients in whom there was a history of bleeding, but in no case could it be claimed that the patient was homozygous, nor was the history of bleeding in these cases as severe as that usually encountered in haemophilia, though this of itself would not invalidate the diagnosis. In Schultz's (1930) case the history of bleeding was compatible

with haemophilia, but all the symptoms disappeared at puberty, and the further history was not recorded. Foulis and Crawford (1934) described a family of which some female members bled after trivial injury and one seemed to have a long coagulation time, but the diagnosis of haemophilia was not established with certainty. The evidence that the patients reported by Davenport (1930), Hoessly-Haerle (1931), Komai (1934), Leak (1934), and Pfenninger (1934) were homozygous female bleeders is unconvincing.

A number of cases have been reported in which a disease clinically resembling haemophilia has developed in women who had previously been healthy. In no case was there a family history of disease (Joules and Macfarlane, 1938; Rosenthal, Vogel, and Beres, 1937; Madison and Quick, 1945; Hewlett and Haden, 1949). In three further cases (Fantl and Nance, 1946; Chargaff and West, 1946; Dreskin and Rosenthal, 1950) circulating anticoagulants had been demonstrated, and the patients reported by Rosenthal, Vogel, and Beres (1937) and Hewlett and Haden (1949) eventually seemed to recover completely. Since the disease in these cases was clearly different from hereditary haemophilia, they need not be considered further.

One further family remained to be considered, in which it appeared that homozygous haemophilic females might exist. It was first described by Treves (1886), and later by Bulloch and Fildes (1911, pedigree 493) and by Handley and Nussbrecher (1935). Through the assistance of Mr. R. S. Handley the author was able to get in touch with this family, who proved most co-operative. The investigations which have recently been carried out leave little doubt that the disease in this family is haemophilia, and that its affected female members are homozygous. Most of the genetic data were recorded in this Journal by Handley and Nussbrecher (1935); the additional facts here presented concern the fifth and subsequent generations.

Techniques

Coagulation time. All tests were carried out at 37° C. In the Lee and White test four 2½ in. × ⅜ in. test-tubes were used, and all were tilted at half-minute intervals until the blood clotted. In the Dale and Laidlaw method fine capillary tubing containing lead shot was filled with blood and tilted until the shot failed to move. In the recalcification of oxalate-plasma, calcium chloride M/40, normal (0·85 per cent.) saline, and plasma were mixed in equal proportions, and the coagulation time was recorded.

Prothrombin consumption (Merskey, 1950 *a*, *b*). In this test the prothrombin present in citrate-plasma is compared with the amount present in the serum one hour after the blood has coagulated in glass tubes. The serum from the Lee and White tubes was used as serum from venous blood; for serum from capillary blood a finger was pricked and blood collected, the finger being squeezed to obtain a mixture of blood and tissue fluid. The prothrombin was measured by a two-stage technique. Brain thromboplastin and M/40 calcium chloride were added to the plasma (or serum) and samples were removed from

this mixture at fixed intervals and added to solutions of fibrinogen in a second row of tubes, the time taken for the second row of tubes to clot being recorded.

Tourniquet test. The sphygmomanometer cuff was inflated to 100 mm. Hg for five minutes, and the petechiae which appeared on the arm were counted.

Correction of coagulation defects of known haemophilic blood. Blood was taken from a known male haemophilic, citrated, and centrifuged at 1,500 revolutions per minute to obtain plasma. Citrate-plasma from the patients to be tested and from the normal controls was obtained in the same way, and dilutions of each sample were made in normal saline. 0·2 ml. of each of these plasma dilutions was incubated separately at 37° C. with 0·2 ml. of known haemophilic plasma and 0·2 ml. of M/40 calcium chloride, and the time taken for the plasma to coagulate was recorded. All tests were performed in duplicate and the results averaged. One hour after coagulation had occurred the amount of prothrombin remaining in each tube was measured.

Normal values (Merskey, 1950*b*). The upper level of normal for the average of the four tubes in the Lee and White coagulation time test is 10 minutes, while 11 minutes is regarded as definitely abnormal. By the Dale and Laidlaw technique 180 seconds is regarded as being outside the normal range. The coagulation time of recalcified normal plasma (slow spun) rarely exceeds 180 seconds. The upper level of normal of the prothrombin-consumption index is 40 per cent., though most normal subjects give readings of less than 20 per cent. In the tourniquet test 10 petechiae or less are regarded as being compatible with normal.

Case Histories

The family tree, brought up to date, is shown in Fig. 2. It will be seen that the affected women occur in the fifth generation, and result from a first cousin marriage in the fourth generation. Much of the history has been published in detail, and only the essential parts of earlier data will be repeated in addition to the relevant history subsequent to 1935. No additional information was available regarding the first four generations. The following patients were seen and examined. Unless otherwise stated, full physical examination disclosed no other signs of disease.

Female patients

V, 5

History. The patient when examined was 67 years old. She had always bled excessively even from small cuts, larger cuts occasionally bleeding for many weeks. She had had repeated epistaxis, and severe bleeding after dental extraction, and bruised very easily. She had had severe menorrhagia until the menopause occurred at 55 years of age, and repeated haematuria. For the last 11 years she had suffered from indigestion compatible with a peptic ulcer, and three years ago she had had haematemesis. She thought a peptic ulcer had been demonstrated by barium meal X-rays, but efforts to obtain more information on this point were unsuccessful. She had had many episodes of haemarthrosis,

involving elbows, ankles, knees, hips, and wrists. The joint swellings were very painful and took weeks to subside.

Examination. Several bruises were found, and there was moderate limitation of movement of her right elbow, left wrist, right hip, and right ankle. X-rays of the joints (Plate 30, Figs. 4, 5, 6) showed severe changes in the left carpal region, with considerable diminution of the articular spaces, irregularity of the surfaces, and slightly increased bone density. The right elbow showed marked enlargement of the articular notch of the ulna due to erosion, some destruction of the head of the radius, and slight periarticular calcification. Similar changes of a lesser degree were present in the right hip, right ankle, and both knees.

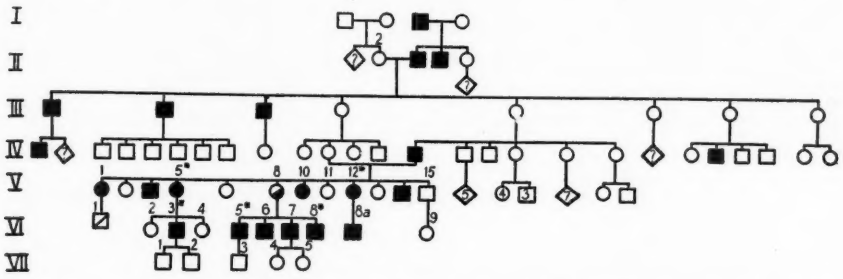

FIG. 2. The family tree (compare Handley and Nussbrecher, 1935, whose numbering is retained) brought up to date by the addition of the individuals VI, 8 a and VII, 1 to 5. The gaps in the numbering are accounted for by the omission of unaffected husbands or wives who, so far as is known, were not otherwise related. Note the first-cousin marriage in the fourth generation and the affected females in the fifth generation.

Males: ■ = affected, □ = unaffected. Females: ● = affected, ○ = unaffected. ◑ = possibly affected. ⍁ = died too young for diagnosis to be established. ◇ = offspring, sex unknown (number enclosed). A symbol enclosing a figure represents that number of individuals. Individuals personally examined by the author are indicated with a *. The results of subsequent investigations in the case of V, 8 are given on page 306.

Laboratory findings (Tables I, II, III, and Fig. 3). The coagulation time measured by the Lee and White method was on the upper level of normal; the capillary blood coagulation time and the coagulation time of recalcified oxalate-plasma were abnormal. There was defective consumption of prothrombin when serum from whole clotted venous blood was used, but not when capillary blood was used. The tourniquet test was positive, and there was inability to correct the coagulation defects of known haemophilic blood. The other laboratory findings were normal.

V, 12

History. The patient when examined was 57 years old, and was said to bleed excessively from cuts and after dental extraction. She had had epistaxis, and bruised easily. She had had menorrhagia and haematuria, but no haematemesis or melaena. There had been episodes of haemarthrosis, which were milder than those of V, 5. The knees, ankles, elbows, wrists, and one hip had been involved; the swellings had only lasted a week or two, and had left no permanent limitation of movement or changes demonstrable by X-rays. Clinical examination disclosed no abnormalities except two bruises.

Laboratory findings (Tables I, II, III, and Fig. 3). These were similar to those of V, 5 except that the Lee and White coagulation time was definitely abnormal, and the tourniquet test faintly positive.

TABLE I

Summary of Laboratory Findings

Date	*Patient*	*Sex*	*Coagulation time and method used*				*Prothrombin consumption index (%)*						
			Lee and White; individual tubes (minutes)	*Dale and Laidlaw (seconds)*	*Recalcified oxalate-plasma ('Quick's test for haemophilia') (seconds)*								
					Slow spun (750 r.p.m. for 5 mins.)	*Fast spun (3,000 r.p.m. for 5 mins. in angle-centrifuge)*	*Venous blood*	*Capillary blood*	*Ivy bleeding time (minutes)*	*Tourniquet test*	*Platelets (per c.mm.)*	*Plasma fibrinogen (mg. per 100 ml.)*	*Plasma prothrombin*
5.2.50	V, 5	F	10; 10; 10; 11¼	293; 205	580	740	100	< 5	1	Positive; 120 petechiae	217,000	320	Normal
5.2.50	V, 12	F	12½; 12½; 12½; 13	332; 230	922	1,162	44	< 5	1	Faint positive; 20–30 petechiae	207,000	140	Normal
23.1.50	VI, 3	M	9½; 11; 11½; 12	165; 195	289	..	35	< 5	..	..	..	..	Normal
5.2.50			12; 9½; 12; 9½	210	595	732	42	< 5	2	Negative	154,000	284	Normal
18.4.50	VI, 5	M	10½; 12½; 10; 12½	185	350	692	64	< 5	2	Negative	250,000	..	Normal
18.4.50	VI, 8	M	11; 12½; 11; 12	190	385	816	64	< 5	1	Faint positive; 15 petechiae	270,000	..	Normal

Conclusion regarding female patients. The clinical history and laboratory findings in the case of V, 5 and V, 12 were those of haemophilia. The haemophilia was of the type associated with a slight prolongation of the coagulation time. The positive tourniquet test in V, 5 and the faintly positive test in V, 12 were anomalous findings.

TABLE II

Tests for Circulating Anticoagulant

All the plasmas had been stored for four days at 4° C. Each plasma mixture was recalcified at 37° C. with an equal volume of M/40 calcium chloride, the test being performed in duplicate, and the results averaged. There is no evidence of a circulating anticoagulant.

	Calcium time of recalcified citrate-plasma (seconds)			
	Patient V, 5	*Patient V, 12*	*Known severe haemophilic*	*Normal control*
Plasma plus normal (0·85%) saline	285	520	380	110
Plasma plus 10% normal plasma in normal saline . . .	210	170	190	..
Plasma plus 20% normal plasma in normal saline . . .	135	145	140	..
Plasma plus equal volume normal plasma in normal saline . .	155	155	155	..

TABLE III

The Effect of the Addition of Patients' Citrate-Plasma on the Prothrombin Consumption Index of Known Haemophilic Plasma (Haemophilic B)

The Lee and White coagulation time of haemophilic A was 13 minutes, while that of haemophilic B was over 40 minutes. The plasma added to haemophilic plasma B was made up to 0·2 ml. with normal (0·85%) saline, and recalcification at 37° C. was effected by the use of M/40 calcium chloride. The calcium times of these tubes appear in Fig. 3. Note the relative inability of all four test plasmas to improve the prothrombin consumption defect of haemophilic plasma, compared with the effect produced by two normal controls. The results obtained with known haemophilic A were similar to those obtained with the plasma of the patients tested in this experiment.

Amount of plasma added to known haemophilic plasma B		*Prothrombin-consumption index (%): serum tested one hour after coagulation*					
Test plasma	*Known haemophilic plasma B*	*Control A*	*Control B*	*Patient V, 5*	*Patient V, 12*	*Patient VI, 3*	*Known haemophilic A*
Nil	100	183	183	183	183	183	183
0·25	99·75	49	28	169	183	183	200
0·5	99·5	17	16	200	183	183	183
1·0	99·0	< 5	< 5	183	122	122	122
2·0	98·0	< 5	< 5	129	138	96	86
5·0	95·0	..	..	110	138	92	129
10·0	90·0	..	..	105	122	59	129
100·0	Nil	< 5	< 5	55	26	< 5	73

Since the preparation of this paper Dr. J. V. Dacie of the Postgraduate Medical School of London has kindly investigated the female patient V, 8, with the following results.

Coagulation time (Lee and White): 13½ minutes.
Prothrombin time: normal.
Clot retraction: normal.
Prothrombin consumption index: 33 per cent.
Platelet count: 210,000 per c.mm.
Bleeding time: 15 minutes.

Her plasma failed to reduce the abnormally long clotting time of plasma from two of her sons. V, 8 therefore has a clotting defect resembling that of the affected male members of the family. Her history as regards bleeding will be found in the Appendix.

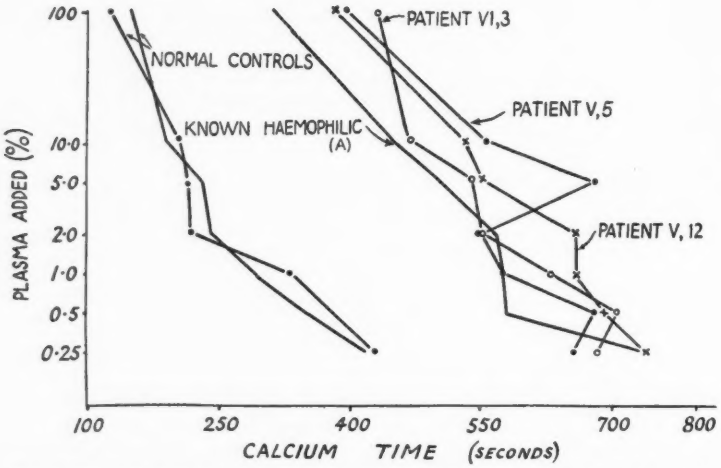

FIG. 3. The effect of the addition of patients' citrate-plasma on the calcium time of known haemophilic plasma (B). Two normal controls and another known haemophilic (A) also appear in the diagram. The prothrombin-consumption index of these tubes appears in Table III. The plasma added has been plotted on a logarithmic scale, the calcium time of haemophilic plasma B being 787 seconds. All tests were done in duplicate and results averaged. Note the relative inability of all four test plasmas to shorten the calcium time of known haemophilic plasma, compared with the effect produced by two normal controls.

Male patients

VI, 3; VI, 5; VI, 8

History. All had essentially similar histories. They had all bled excessively from cuts, and bleeding sometimes continued for many weeks. They all bruised very easily, had had repeated epistaxis, and had bled severely, sometimes for a month or more, after the extraction of teeth. VI, 8 alone had been free of haematuria. VI, 3 had had haemarthrosis involving both knees, both ankles, and both elbows. These attacks lasted many weeks and had left some permanent ankylosis in both knees, in one elbow joint, and to a lesser degree in both ankles. A year ago he had been involved in a car accident, fracturing the left femur and two ribs; he then developed a haemothorax, and one leg was discoloured from the thigh to the foot. He had made an uneventful

recovery. VI, 5 had had haemarthrosis of the left shoulder and, after injury, of the left ankle and the right elbow. There were no permanent deformities, but he said that the joints often felt stiff and painful. VI, 8 had had a haemarthrosis of the right elbow following injury. There were no permanent joint deformities.

X-rays. In VI, 3 there are erosion of the articular surfaces, loss of joint space, and increased bone density in both knees, the left elbow, and both ankles. The lower end of the femur and upper end of the tibia show pseudocyst formation, more marked on the left side (Plate 31, Figs. 7, 8).

Laboratory findings (Tables I, II, III). These were essentially the same as in the female patients. The Lee and White, and Dale and Laidlaw, coagulation times were on the upper border of normal and the coagulation time of recalcified plasma was abnormal. Normal readings were encountered in all three patients when serum from capillary blood was used for measuring the consumption of prothrombin during coagulation; when venous blood was used the readings were abnormal in two patients, and on the upper border of normal in the third. The plasma of this last patient was tested in its ability to correct known haemophilic blood, and was found to be less effective than normal plasma (Fig. 3). A faintly positive tourniquet test was encountered in one patient. The other laboratory findings were normal.

Conclusion regarding male patients. The clinical history and laboratory findings in these three patients were those of haemophilia. The findings were similar to those encountered in the female patients, the faintly positive tourniquet test in one case being the only anomalous feature.

Additional information regarding other members of the family will be found in the Appendix. None of these patients were examined or interrogated, the information being obtained either from those members who were examined or by correspondence.

Discussion

Haemophilia is a well-defined state, and apart from genetic considerations certain clinical and laboratory findings constitute the criteria upon which its diagnosis should depend. These are (*a*) a tendency, present from early infancy, to bleed excessively after trivial injury, and after the first few years of life haemorrhage into the joints; (*b*) a delay in the coagulation, but no quantitative alteration in the platelet, prothrombin, fibrinogen, or calcium content of the blood; (*c*) the absence of any cause for the haemorrhagic tendency other than the defective blood-coagulation (Joules and Macfarlane, 1938); (*d*) to these findings may be added a normal content of plasma factor v, defective consumption of prothrombin during coagulation, and an inability of the blood to correct the coagulation defects of known haemophilic blood. In any particular case these criteria may not all be fulfilled. Various grades of the haemophilic defect appear to exist; cases have been described with a normal coagulation time, and even with a normal degree of consumption of prothrombin during coagulation (Merskey, 1950*b*). In such cases there has been some ability to correct the coagulation defects of known haemophilic blood, but this ability has not

been as great as normal. This effect on haemophilic blood can be used as the deciding test in doubtful cases.

Clinical syndrome. The clinical syndrome in the female as well as in the male members of the family described is that of haemophilia. The disease started early in life, the patients have all bled excessively from small or large wounds, and haemorrhage has occasionally continued for weeks. The easy bruising, the frequent epistaxis and haematuria, and especially the attacks of haemarthrosis resulting in permanent joint deformity, are all met with in haemophilia. The association of haemarthroses with a familial haemorrhagic disease is almost pathognomonic of haemophilia. Rare cases associated with circulating anticoagulants have been described, in some of which haemarthroses have occurred (Soulier and Burstein, 1948), and there have been occasional references to haemarthrosis occurring in pseudo-haemophilia (Rosenfeld, 1921; Little and Ayres, 1928; Weeks, 1934; Halliwell and Brigham, 1948); but haemophilia associated with a normal coagulation time has not been excluded in all these cases.

Laboratory findings. The laboratory findings were those of haemophilia with the coagulation time only slightly prolonged. The figures for the coagulation time were a little in excess of normal when measured with venous blood, and considerably in excess of normal if measured with capillary blood. The consumption of prothrombin during coagulation was abnormal when measured with venous blood, and normal when measured with capillary blood (Table I). The plasma of these patients was unable to correct the coagulation defects of known haemophilic blood to a degree at all approaching the ability of normal plasma (Fig. 3 and Table III). In the absence of a circulating anticoagulant (Table II) these findings are virtually diagnostic of haemophilia. The only laboratory findings which were not typical of haemophilia were the positive tourniquet test in one patient and a faintly positive result in another two. Handley and Nussbrecher (1935) also reported a positive test in the case of V, 5. In a series of 54 haemophilics previously reported (Merskey, 1950*b*) a positive tourniquet test was only encountered on one occasion. With the exception of the positive tourniquet test, the laboratory findings in the patients of the present series were those of haemophilia with slightly prolonged coagulation time. Cases of haemophilia with a normal or nearly normal coagulation time have been previously described (Merskey, 1950*b*, 1951). In a series of 54 haemophilics there were nine in whom the Lee and White coagulation time was under 10 minutes, while in a further 12 it was between 10 and 15 minutes. When the coagulation time was not prolonged, the prothrombin-consumption defect was less than that found in classical haemophilia; the plasma of such patients was able to improve the coagulation defects of known haemophilic plasma to some extent, but this ability was much less than that of normal plasma. These laboratory findings remained relatively constant from year to year, and the short coagulation time was not a temporary fluctuation towards normal. In all other respects the disease in such cases resembled haemophilia. It was confined to males, and was inherited in a sex-linked recessive manner.

The symptoms were those of haemophilia, although in some cases they tended to be rather less severe. The syndrome appeared to breed true in any one family, even over a number of generations. All these patients, as well as those described in the present paper, seemed to have the haemophilic defect, but to a lesser degree.

Genetic considerations. It was mainly from genetic considerations that Bulloch and Fildes (1911) and Handley and Nussbrecher (1935) rejected Treves's (1886) original contention that the disease in the family under discussion was haemophilia. In the early stages the inheritance was certainly not that of haemophilia, there being apparently direct transmission of the disease from father to son in the first four generations. The inheritance in later generations is compatible with haemophilia. On theoretical grounds the offspring of a marriage between a haemophilic man and a carrier woman should include equal numbers of haemophilic and normal male children, and of haemophilic and carrier female children (Fig. 1, iii). It is impossible for such parents to produce a normal (non-carrier) female child. The children resulting from the first-cousin marriage in the fourth generation of this family consisted of (*a*) four affected (? homozygous) females; (*b*) one carrier (heterozygous) female (V, 8)—it is possible that she, too, should be regarded as a homozygous female;[2] (*c*) one apparently normal female (V, 11)—since she had no children, it is impossible to say whether she was a carrier or not; (*d*) two affected males and one normal male. The other children did not survive infancy. All these children could result from the marriage of a female carrier of haemophilia and a haemophilic man. If the four affected females were homozygous for haemophilia, they could produce only haemophilic sons or carrier daughters (Fig. 1, iv). VI, 1 died at the age of 14 weeks of diarrhoea, and both VI, 2 and VI, 4 died in infancy. All the other male children of these four women are affected, and there are no other female children. The four affected women may therefore be homozygous for haemophilia. The sons of the affected males are all apparently normal, as would be anticipated in haemophilia. The daughters also appear to be normal. As the children of the seventh generation are still very young, one cannot be certain whether they are affected, but there is nothing in this generation so far which is incompatible with the diagnosis of haemophilia in the family. The only obstacle to the diagnosis of haemophilia is the inheritance of the disease as described in the first four generations. The patients in question all died many years ago, the history of bleeding in them is very scanty and, especially with regard to the first, second, and fourth generations, often amounted to no more than a tradition in the family that they were bleeders. The history of bleeding in the third generation is a little more convincing. This is of interest in that the transmission would then be compatible with II, 2 being a carrier. Bulloch and Fildes inquired of the doctors in the Saffron Walden district, where members of the family had long resided, but could obtain no helpful information. A search of the London Hospital records in 1910 also disclosed discrepancies with Treves's original report. It will serve no useful purpose at the present time to attempt

[2] For further evidence see page 306.

to prove or disprove the inheritance as described in the first four generations, since no additional information is available. The disease as now seen, with its inheritance in recent years, is indistinguishable from haemophilia, so that either the anomalous type of inheritance described can occasionally occur in haemophilia, or the record is incorrect. Cases of haemophilia with transmission of the disease from father to son have been described by Snyder (1932) and by Wright, Doan, Dodd, and Thomas (1948). In both instances it was assumed without other evidence that the wife was a carrier of the disease. Gates (1946) was prepared to accept the theory that this type of inheritance can occur in haemophilia if the disease is originally carried on the Y chromosome. His arguments are not very convincing. Whatever the explanation, it does not invalidate a diagnosis of haemophilia in the family under discussion, and of the homozygous haemophilic state in the female patients described above.

Acknowledgements

My thanks are due to Dr. A. H. T. Robb-Smith, Director of Pathology, Radcliffe Infirmary, to Dr. R. G. Macfarlane in whose department the present study was carried out, to Dr. R. G. Macfarlane and Dr. Rosemary Biggs for constant advice and encouragement, and to Miss J. Lash for technical assistance. I am indebted to Dr. J. V. Dacie, of the Postgraduate Medical School of London, for the laboratory investigation of the patient V, 8, to Dr. R. A. Kemp Harper, of St. Bartholomew's Hospital, for the X-rays, and to Mr. R. S. Handley for putting me in touch with the family. The expenses of the investigation were defrayed by the Nuffield Foundation Haematology Research Fund and the Medical Research Council, and the author was in receipt of a personal grant from the Cecil John Adams Foundation (South Africa).

Appendix

V, 8 is said by her sons to be aggrieved that she is not figured as a bleeder, since she thinks she is as much affected as V, 12, though not so badly as V, 5. She bruises very easily, and has trouble with her joints, which 'swell up after injury'. The joints involved are the ankles, knees, and shoulders. She bled quite severely when teeth came out spontaneously, and is afraid to have any teeth extracted.

V, 10. Her history is similar to that of the other affected female patients. She died recently of 'heart disease', but it was observed in her terminal illness that her neck and thorax became swollen and black, and VI, 3 suggested this might be due to intrathoracic haemorrhage. There was no autopsy.

V, 11 has no trouble with bleeding. She bruises a little, but cuts do not bleed excessively. She has had all her teeth extracted without excessive haemorrhage, and has had no trouble with her joints.

V, 15 has no trouble with bleeding.

VI, 1 died at the age of 14 weeks.

VI, 2 and VI, 4 died in infancy.

VI, 6 and VI, 7 are both affected in a similar manner to their brothers VI, 5 and VI, 8; VI, 6 is the least affected of the four.

VI, 8a. Aged 14 years. At birth he bled for 14 days from the umbilicus. He bruises excessively, bleeds profusely from cuts and scratches, and has had repeated epistaxis and haematuria. He has intermittent swellings of the ankles and knees. These swellings are very painful and take weeks to subside.

VI, 9. Aged 18 years. She has no trouble with bleeding, and has had teeth extracted without excessive haemorrhage.

VII, 1, aged five-and-a-half years; *VII, 2,* aged two years; *VII, 3,* aged three years. All are apparently normal, and do not bleed excessively even from quite severe cuts.

VII, 4, aged eight years, and *VII, 5,* aged three-and-a-half years, are both said to be normal.

Summary and Conclusions

In 1886 Treves described a family of haemophilics in which some females appeared to be affected. This family, of which the most recent report up to the present was that of Handley and Nussbrecher (1935), has been investigated again, and the inheritance of the disease has been traced to the seventh generation.

The clinical history and laboratory findings are those of haemophilia. The affected female members of the fifth generation have all the clinical and laboratory manifestations of the disease. The severity of the clinical syndrome and the degree of haematological abnormality in these women do not appear to be different from those found in the affected male members of the family. Since they were the children of a male haemophilic and his first cousin, this unusual occurrence of affected female members in a haemophilic family can be explained by assuming that their mother was a carrier, and that they were homozygous for the disease.

The only anomalous laboratory findings were a positive tourniquet test in one female and a faintly positive result in one female and one male patient. The haemophilia was of the type in which the coagulation time is only a little prolonged. It is impossible to explain fully the anomalous inheritance in earlier generations. Either this type of inheritance can occur in haemophilia, or the record is incorrect. The inheritance in later generations is of the classical type in haemophilia. The subsequent generations are all compatible with a diagnosis of the homozygous haemophilic state in the affected women, who appear to be the first human female subjects in whom the diagnosis of haemophilia has been substantiated. Treves's original diagnosis of haemophilia in the female would thus appear to be correct.

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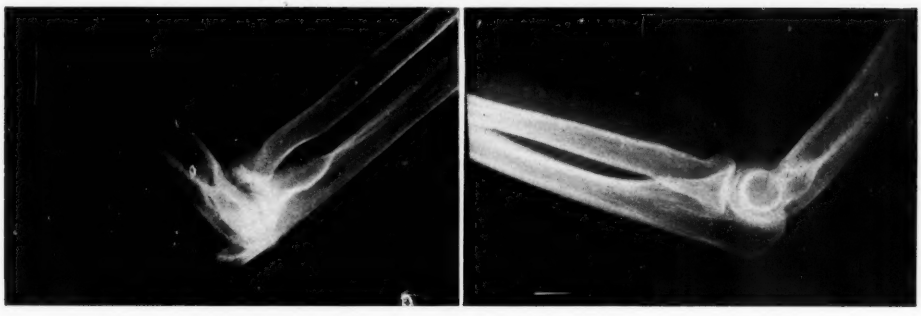
FIG. 4. X-ray of carpal region of V, 5. Note severe changes in the left carpal region, with considerable diminution of the articular spaces, irregularity of the surfaces, and slightly increased bone density

FIG. 5



R FIG. 6 L

FIGS. 5 and 6. X-ray of elbows of V, 5. On the right side note enlargement of the articular notch of the ulna due to erosion, and some destruction of the head of the radius

R FIG. 7 L

FIG. 8

FIGS. 7 and 8. X-ray of the knee-joints of VI, 3. Note the erosion of the articular surfaces, loss of joint space, and pseudocyst formation, more marked on the left side

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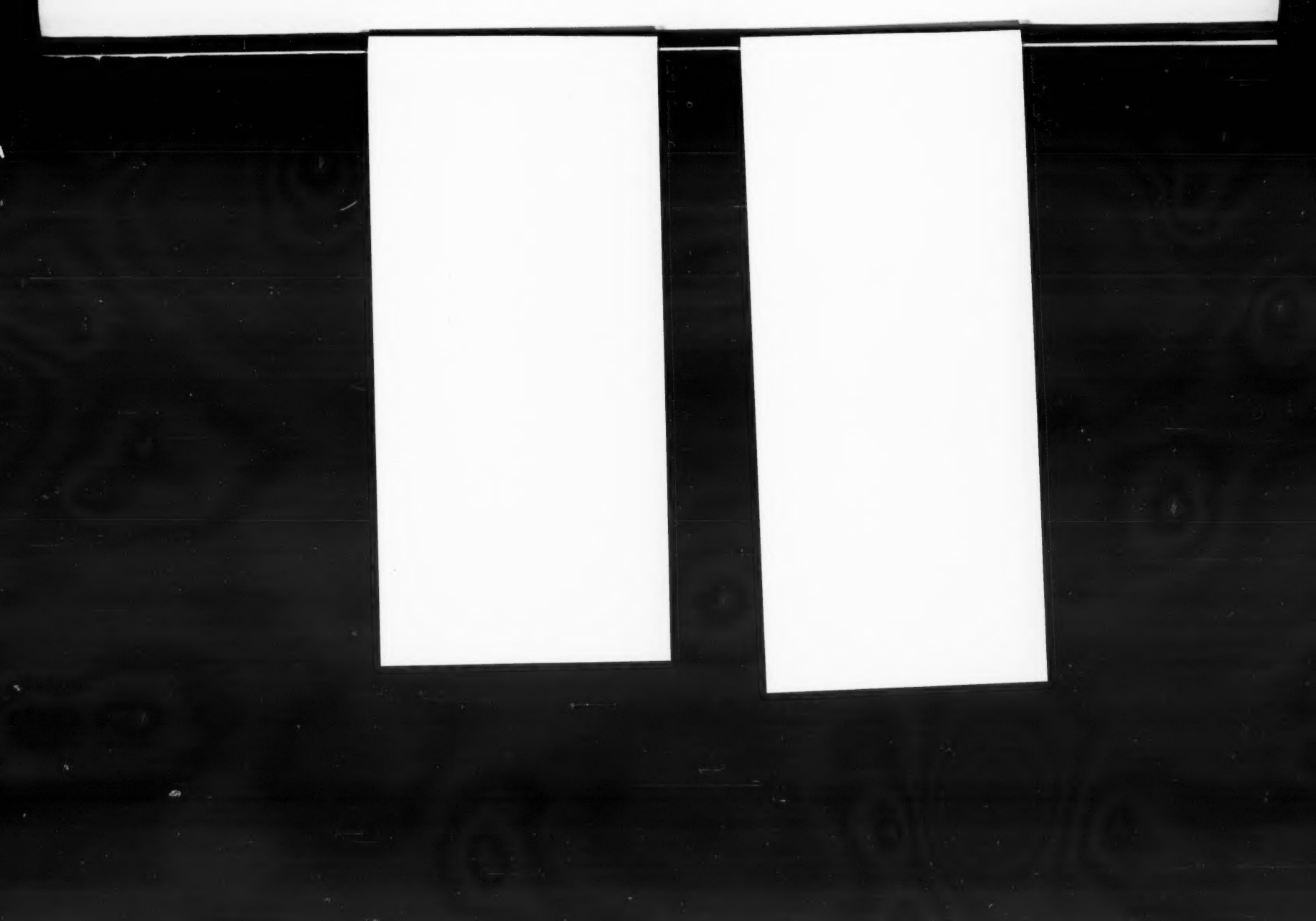

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ARTIFICIAL PNEUMOTHORAX[1]

A Survey of a Personal Series

By FRANK SCADDING, HOWARD NICHOLSON, and CLIFFORD HOYLE

(From the Brompton Hospital, London)

Artificial pneumothorax has been so much used that there might seem little reason for recording a small group of patients treated in this way for pulmonary tuberculosis. The literature, already vast, has surveyed most of the ground repeatedly: the suitable patient, the responsive forms of disease, the time for induction, the technical management, the auxiliary procedures, the right duration, and the complications, course, and results. Latter years have seen less writing on the subject with more repetition, almost as though there were an accepted code of opinion. Indeed, a sense of confidence about the range and conduct of treatment by pneumothorax has in many ways appeared to be abroad at last.

Yet good judges have continued to point out that such a summary of the situation is scarcely true. They agree that most of the early hazards, and even the main risks of pyothorax and bronchopleural fistula, have been largely overcome by restricting the choice of candidates and by better tactics. A few still dissent from the division of adhesions, though admitting the importance of the kind of relaxation of the lung that is achieved. Many more, with surgery in mind, doubt the wisdom of pneumothorax treatment at all, even where before it would have been thought to offer a fair prospect of success. This is not the only way in which the problem of the right choice of treatment can be raised. Critics feel that treatment by pneumothorax is coming more and more under review, less from doubt of its success than from their own belief that this success is often fortuitous and may be excelled by other methods. They feel that the conditions for success need to be better understood for pneumothorax to resist the challenge of other measures. They feel, too, that the doubts already curb its use.

There are in fact many doubts, and they affect a surprisingly wide variety of technical issues. What, for instance, are the bearings of the site and type of disease on the risks and outcome of the treatment? How far do undivided adhesions prevent success? Is an atelectatic[2] segment or lobe a serious matter in the long run? Does an early effusion, however small and benign, mean a greater risk of more pleural infection later on? Is the course of an effusion dependent mainly upon the state of affairs in the lung? For how long should a good pneumothorax be kept, and when does the risk of losing respiratory

[1] Received March 9, 1951.

[2] Atelectasis implies etymologically that the lung has never been aerated. By usage it has come to mean airlessness, and we use it in this sense.

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efficiency exceed the risk of relapse? On the answers to these questions, at least, critical and experienced writers are not agreed.

It follows that one of the main problems in reviewing the literature is to understand why the collective effect of the mass of records available has not led to agreement. One can see how early views, as well as those from the adolescence of pneumothorax treatment, have been largely superseded as experience grew. Moreover, a controlled investigation was never made in the early days, so that the subject was left much more open than it might have been to vicissitudes of opinion. The advent of the surgeon has intensified them. Although he has made pneumothorax more efficient and has offered alternatives, his criticisms are biased because they spring almost wholly from experience of its failures. We believe that all these reasons have helped to widen the rifts in opinion, without accounting for them entirely.

One other reason has been disregarded. This is that most of the lengthy series in the literature have the same principal flaw as material for analysis: they lack the uniform structure required of an assessable clinical group. This is because they consist of results collected from different centres, compiled in retrospect, so that standards of assessment bear the motley quality conferred by varied supervision. Deductions from such material may be fallacious, whatever the strength of the mere numbers concerned. They often fail to agree because each series is devoid of uniform assessment within itself—a common fault which we believe contributes greatly to discrepant results. Because of this fallacy in the literature the present investigation was made, for we had an opportunity to collect, and to supervise continuously at one clinic, a series of patients treated by pneumothorax. It comprises those patients whose treatment began at the Brompton Hospital under the care of one of us (C. H.) and was continued there at his clinic. As it includes only those whose plan of treatment the authors have decided and have conducted throughout, it is a small series (50 patients). All the itinerant population of the clinic (311 others) are omitted. There are no controls, for we are not primarily concerned here to compare pneumothorax with other forms of treatment. Moreover, the provision of controls would have meant a far wider undertaking, which could only have been justified had there been substantial reasons for believing that treatment by pneumothorax was either useless or harmful, or that it could be withheld from patients likely to benefit. Our aim was the less ambitious one of describing the events in a personal series.

Literature

Few published series bear much similarity to the present group of patients. Even the fine survey by Bentley (1936), dealing with 677 patients treated by artificial pneumothorax, was compiled from the work of many physicians. Adhesions were rarely divided, and less than half of the patients had a satisfactory pneumothorax. His paper and that by Sinding-Larsen (1937) are two of the most exhaustive of the many dealing with collected material. Since such material is not comparable to ours, we shall refer only to accounts of patients

in the care of one physician or of a small group of physicians at a single institution. One of the earliest, by Edouard Rist (1927), dealt with the results of treating unilateral pulmonary tuberculosis. Seven hundred and fifty-nine patients were treated in the 13 years before 1926, in the Laennec Hospital for their first few months, and later at the dispensary. Fifty-two per cent. were well, either with healed disease after completion of treatment or, if still under treatment, free from symptoms and at work. The other 48 per cent. were dead or were unaffected by treatment, or had had extension of disease to the other side. Fifty-one of those treated successfully had had their pneumothoraces terminated, though the pneumothorax had lasted longer than three years in only 16. Those who were well but still under treatment totalled 336, of whom only 28 had been followed for more than five years. Burrell recorded his results in 1933, and later (1935) followed his patients to 1934. He dealt with 299 patients treated between 1918 and 1925. They were classified by the extent of disease in the contralateral lung into patients (1) with no signs of active disease in the better lung, (2) with signs of slight disease in the better lung, and (3) with a third or more of the better lung involved. The proportion with arrested disease in each of these groups was 53, 16·4, and 4·4 per cent. respectively. These figures, coming from an early series, leave unanswered the question how far better radiological control and early division of pleural adhesions might have affected them. Cedric Shaw (1933) investigated the records of 267 patients in the care of Batty Shaw at the Brompton Hospital between 1922 and 1930. All except 14 had their pneumothorax induced in the hospital. The main purpose of the study was to compare the results of artificial pneumothorax with those of sanatorium management alone. The results at Batty Shaw's clinic were matched against those obtained at the King Edward VII Sanatorium, Midhurst, published by Bardswell and Thompson in 1919, using the same classification. Group I comprised incipient cases, with slight infiltration and few symptoms; Group II those with more extensive infiltration, but no obvious cavitation; and Group III far advanced cases. Judged by mortality alone, the results of artificial pneumothorax were much the better. Ninety-three per cent. of patients in Group I were working, 79 per cent. of Group II, and 36 per cent. of Group III. A comparison of this series with our own would have been valuable, as each was in the care of a physician at the same hospital; but there are differences which preclude it. Our patients were observed for at least five years from induction of the pneumothorax, many of Shaw's for a much shorter time; and only five of his had their pleural adhesions divided. An earlier paper by Trail and Stockman (1932) dealt with 91 patients at the King Edward VII Sanatorium, Midhurst, in whom artificial pneumothoraces were induced between 1927 and 1930. They were classified by the extent of disease, and the best results were found when the disease was limited and recent. Later, Trail (1934) analysed the results in 80 patients whose artificial pneumothoraces were induced between 1924 and 1930, and whose refills had ceased. Thirty-three other patients selected for treatment by artificial pneumothorax, in whom it had not been achieved successfully, were also followed for the same period.

Fifty-one of the 80 with pneumothoraces were fit for work, but only six of the other 33. One-fifth of the pneumothorax group had died, and two-thirds of the others. Forty of the 80 patients with pneumothoraces had effusions, though without apparent effect on the outcome. This paper was widely quoted and valuable at the time, but lacks a definitive quality for several reasons. Details of the pneumothoraces are omitted, the results are unrelated to the type and extent of pulmonary disease, and adhesions were not usually divided. Nor can the untreated group be regarded as fair controls. Another series treated at one institution was described briefly by Jennings, Mattill, and Nemec in 1940. They dealt with 1,027 patients in whom treatment by pneumothorax was attempted before January 1937 at Glen Lake Sanatorium. A satisfactory pneumothorax was obtained in 321, of whom 81·9 per cent. resumed work. They were followed for periods of from one to 20 years. Three hundred and forty-six others had a pneumothorax 'insufficient to affect either the symptoms or lesion'. Only 23·1 per cent. of these patients resumed work. Except for this grouping in terms of the effectiveness of treatment, no further information was given. In 1941 Bloch, Tucker, and Adams gave a most extensive review of the literature, covering 2,100 publications dealing with artificial pneumothorax, among which were 99 concerned with results. Not more than 34 of these were thought to give adequate indication of the standards by which the success or failure of treatment could be judged. They then described their own results in 60 patients treated at the University of Chicago Clinics. Their criteria of successful treatment, taken together, were strict: complete re-expansion of the lung; adequate radiographic evidence of healing, including closure of cavities; ability to return to normal life; and persistent absence of tubercle bacilli from the sputum, and of all signs of active disease, including extrapulmonary complications. No patient was regarded as cured until these conditions had all been fulfilled for at least two years. Only 19 of their own 60 patients satisfied this standard, and all were initially regarded as 'favourable cases'. A series recorded by Morriss in 1942 dealt with 370 patients treated by artificial pneumothorax at Gaylord Farm Sanatorium and its out-patient department. Sixty-six per cent. were doing full-time work; 20 per cent. had died. The observations covered an average period of five and a half years after termination of the pneumothoraces. Ineffective collapse was among the most unfavourable influences on the result of treatment. A large effusion, the chief complication, occurred in 29 per cent., and one in four of such effusions became purulent. The mortality from empyema was 3·5 per cent. Once again, as in previous series, pleural adhesions were very rarely divided, and nearly one-third of the patients treated did not have cavities; these are important matters in drawing conclusions from their results. Recently, in opening a discussion at the Royal Society of Medicine, Young (1949) compared the results of treatment by artificial pneumothorax in three groups of patients —those under his general supervision at Brompton Hospital, those in his immediate care at St. Bartholomew's Hospital, and his private patients. The incidence of a complicating tuberculous empyema was considerably higher in the Brompton Hospital group than in the other two. He showed that in this

respect, as well as in the final results, his second and third groups, who were under the direct care of one physician throughout their treatment, fared much better than the others. Many patients in his first group had had their pneumothoraces begun elsewhere, and they were never satisfactory. Young's paper is almost the first in the literature to show by its comparative figures the importance for success of continuity of supervision.

The Present Investigation

Clinical Material

The series consists of 50 patients, in whom 54 artificial pneumothoraces were induced at Brompton Hospital between 1935 and 1944, and who were then observed for at least five years up to May 1949. It includes only those who

TABLE I

Age and Sex

Age-group (years)	*Male*	*Female*	*Total*
10–19	1	4	5
20–29	12	23	35
30–39	7	3	10
40–49	3	..	3
50–59	..	1	1

remained continuously in the care of one of us (C. H.) throughout the observations. Except in this respect, and but for the fact that they were thought to be suitable for, and in need of, treatment by pneumothorax, the patients were not selected. Four had bilateral pneumothoraces, each contributing two to the series. The patients were all British, living either in London or its environs. Their occupations could be roughly classified as sedentary (22), non-sedentary (16), and mixed (12); we did not think there was any point in detailed analysis, since no occupation specially predisposing to pulmonary tuberculosis was met. There were 21 male and 29 female patients. Their ages ranged from 13 to 50 years, with a big majority between 20 and 30 years (Table I). Excluding a calcified primary complex, 14 had evidence of previous tuberculosis. Ten of these patients already had a pneumothorax on one side; two gave a history of dry pleurisy on the same side a year before; one had had tuberculous cervical adenitis nine years before; and one other was known to have had pulmonary tuberculosis affecting the other lung for four and a half years. At a rough estimate from the histories and radiographs, the disease for which the pneumothoraces in this series were induced had been active for about six months or less in 32 of the 54 lungs at risk. The least duration of symptoms was a month, the longest three years, and the average eight months. The onset was insidious as a rule (46 out of 54 cases), but acute in eight.

Assessment at Time of Induction of Pneumothorax

Clinical condition. The degree of constitutional disturbance, the severity of focal symptoms, and the amount of sputum were usually slight (Table II). Cough

and sputum were the common symptoms (47 cases), haemoptysis (15 cases) and dyspnoea (10 cases) much less so. Pain, an important symptom as will be seen, was reported by 13 patients. Only four of the 47 with sputum had more than two ounces daily. Tubercle bacilli were found by smear or culture in 34 cases. Between diagnosis and induction 11 patients deteriorated clinically, and 16 radiologically. Although most of these patients had had cavities initially, five had lost ground in the absence of cavitation and in spite of rest in bed.

Radiological appearances. The disease was unilateral in 24 cases (in 15 on the left and in nine on the right) and bilateral in 30. As a rule lateral films and

TABLE II

Initial Clinical Condition

	Nil	*Slight*	*Moderate or severe*
Constitutional disturbance	8	39	7
Focal symptoms . .	3	45	6
Amount of sputum . .	7	43	4

Constitutional symptoms were considered slight when the general condition was good, the loss of weight less than 5 lb., tachycardia less than 90 per minute, and pyrexia less than 100° F., with no sweats. They were considered marked when the loss of weight was more than a stone, and when there were repeated night sweats, pallor, pyrexia more than 101° F., and tachycardia more than 110 per minute. The moderate group was between the two. Sputum was considered slight when less than 2 oz. daily.

tomograms were not taken of the early patients, and even with the help of such films later the segmental distribution of the disease was often uncertain. We have therefore kept to the accepted zones for defining radiologically the extent of disease, which was as follows on the side subsequently treated by pneumothorax:

Involvement of one zone	11 cases
Involvement of two zones	30 cases
Involvement of three zones	13 cases

Judging from radiographs taken just before induction, there were 18 cases of active infiltration without a demonstrable cavity, and 36 with cavitation. Five showed an area of consolidation, two some degree of atelectasis, two considerable fibrosis, and two others some calcification. Of the 36 cases with cavitation 18 had a small cavity up to 2 cm. in diameter, 15 had a moderate-sized cavity 2 to 5 cm. in diameter, and three had a single cavity or total cavitation more than 5 cm. in diameter. Direct evidence of tuberculous bronchitis was scanty, because patients were seldom bronchoscoped until the latter part of this study. In retrospect, however, it is probable from the presence of atelectasis and from the type of cavity, taken with the clinical signs, that five patients had bronchial disease. All five ran an eventful course.

Rest prior to induction. The length of rest in bed before induction of the pneumothorax was calculated for each patient in order to see whether it affected the risk of pleural effusion. Table III shows that there was no preponderance of

effusions among patients who had little preliminary rest. Eighteen patients had three weeks or less of rest in bed between diagnosis and induction; only one developed more than a trace of pleural effusion within six months. All 18 had recent active infiltration, 12 with cavitation; 16 had disease in at least two zones of the lung. Neither the type nor the severity of effusions seemed referable to the duration of initial rest in bed. Nine patients in all had troublesome

TABLE III

Rest in bed before induction (weeks)	0	1	2	3	4	5	6	7	8	9	10	12	18	22	25
Number of A.P.s.	5	3	6	4	8	5	3	2	4	2	4	3	2	1	2
Number of A.P.s developing fluid (more than a trace) within 6 months	0	1	0	0	2	2	1	0	1	1	2	0	1	1	0

effusions, leading either to premature expansion of the lung or to empyema. Yet none of them had had an unduly brief rest in bed before the pneumothorax.

Course of Pneumothorax

A. *Pleural Adhesions and their Thoracoscopic Section*

Pleural adhesions were known to be present in 45 of the 54 cases. Of the other nine, two were found to be free from adhesions by thoracoscopy, and the other seven were assumed to be free on the evidence obtained from screening and from radiographs, together with the favourable response of the disease to the treatment. In 19 patients the adhesions were extensive, in 13 moderately extensive, and in 13 limited. The probability of finding extensive adhesions

TABLE IV

Division of Adhesions

	Number of cases	*Thoracoscopy not done*	*Complete division*	*Partial division*	*Adhesions indivisible*
Extensive adhesions	19	4	1	13	1
Moderately extensive adhesions	13	1	6	6	0
Limited adhesions	13	3	8	1	1

was closely related to the occurrence of pain as a preceding symptom. Twelve out of 13 patients who had had pain in the chest were found to have adhesions, extensive in 11 cases. No patients with limited adhesions, and only one of those with moderately extensive adhesions, had had pain as a symptom. Thoracoscopy, with a view to division of adhesions, was done usually within two months of induction; there were a few exceptions, as when fine adhesions became apparent only after several months. In all cases the adhesions were believed to be preventing collapse of the affected part of the lung. Table IV gives the results in the three groups defined above. Of the patients with extensive adhesions

nine had thoracoscopy once, five twice, and one four times; complete division of the adhesions was achieved once only, two other patients gaining some further relaxation of the lung by a subsequent phrenic nerve crush. Eight with moderately extensive adhesions had a single thoracoscopy, four others needing two operations; two of the 12 had a supplementary phrenic nerve crush. None of those with limited adhesions had more than a single thoracoscopy. The effects of division of adhesions will be discussed later.

Complications of thoracoscopy and division of adhesions (occurring within a month of operation). 1. *Atelectasis.* There were 44 thoracoscopic operations for division of adhesions. Atelectasis of the lung followed on 15 occasions, or about one in three; it was total in 12, and lobar in three only. But the most interesting and, from the prognostic point of view, the most important feature was the rapidity with which the lung became aerated again. In nine cases regular refills were resumed within a month, and in four others in the next few months. Only two patients retained the atelectasis completely and permanently. One of them was found to have tuberculous bronchitis, while the other soon produced a pyothorax. Adhesions had been extensive or moderately extensive in 12 of the 15 cases. The three in which they were limited had only transient atelectasis. No correlation could be found between the amount and character of the sputum at the time adhesions were divided and the occurrence of a 'black' lobe or lung afterwards. Most of these patients had only a little sputum, and others in the series with more sputum escaped the complication. Nor did there appear to be any relation between the facility with which the lung became aerated again and the amount of sputum at the time.

2. *Pleural effusion.* A trace of pleural fluid, below diaphragm level, was seen in six cases; in all these it was absorbed without incident during the next few weeks. In eight other cases, all with extensive or moderately extensive adhesions, there were progressive effusions, of which five became purulent. The appearance of the pleura at operation was either not commented on, or was described as normal (17 cases); pleural tubercles were observed once only, and in this case the pneumothorax was complicated by tuberculous empyema within two months.

3. *Other complications.* The only other serious complication, encountered in one patient, was haemothorax with a bronchopleural fistula. It resulted in a secondarily infected tuberculous pyothorax.

B. *Type of Pneumothorax*

We used a simple classification of the type of pneumothorax eventually obtained, expressing the degree of relaxation of the diseased lung. Such a classification is open to criticism as arbitrary, but it seemed to us the best way of conveying the essential distinction between one pneumothorax and another. The types of pneumothorax and the number of each type were as follows:

Complete pneumothorax: a free lung with no adhesions . .	24 cases
Adequate partial pneumothorax: adhesions present, but not apparently interfering with relaxation of the diseased area .	5 cases

Inadequate partial pneumothorax: adhesions present and interfering with relaxation of the diseased area . . . . . 25 cases

We shall refer later to the fate of the patients in each group.

C. *Complications*

1. *Atelectasis.* Seven patients had atelectasis of the lung after induction, unconnected with thoracoscopy or division of adhesions. In two it was total, in three lobar, and in two segmental. In three the lung became aerated again within a few weeks, but in two this took several months. Even permanent atelectasis of the upper lobe did no harm to the remaining two patients, or to the course of their pneumothoraces.

2. *Non-cumulative effusions.* Fifteen small effusions, no higher than the dome of the diaphragm, were not thought to need treatment. Appearing within a few weeks of induction, nine persisted up to three months, four for several months, and two recurred throughout the course of treatment. Only four of the 15 led to obliterative changes, with undesirable or premature abandonment of a pneumothorax.

3. *Cumulative effusions.* In 15 other pneumothoraces pleural fluid reached a level higher than the diaphragm and interfered with treatment. Eight of these effusions followed close upon the division of adhesions. In 13 the onset was insidious. Six appeared within three months, another five within a year, three between one and two years, and one after a longer period. Cumulative effusions were commoner when there were persisting adhesions; they appeared in only four patients with an apparently free lung. With extra rest and periodic aspiration four disappeared after a few months; two others recurred at intervals harmlessly. The other nine remained, and led to premature obliteration of the pneumothorax, or to a tuberculous empyema. The presence of adhesions appeared to increase the risk of effusion, and the risk that it would be purulent. Persisting cavitation and active disease in the lung seemed to increase the chance of effusions appearing early (always within eight months of induction). Those which formed when disease in the lung was thought to have been controlled did so, as a rule, later (four in six after one year).

Character of the fluid and its effect. Of the 15 cumulative effusions, one began as a haemothorax following the division of adhesions. One other was not examined, but the rest began as clear serous fluid, which remained serous and sterile on culture in six cases. One of these six effusions obliterated the pneumothorax in five months, and the disease in the lung then became active again. But with the others no great difficulty was found in keeping the pneumothorax for as long as required, although three of them had some basal obliterative changes. Eight of the 15 cumulative effusions steadily became tuberculous empyemas. One of these (the one in which division of adhesions led to a haemothorax and bronchopleural fistula) became infected with *Staphylococcus pyogenes*, and required open drainage before a four-stage thoracoplasty. Four of the eight patients died, one from spreading disease after the second stage of a thoracoplasty, one, who repeatedly refused thoracoplasty, from toxaemia, and

two from relapsing disease in the other lung. Of the four patients with empyemas who survived, one did well after a four-stage thoracoplasty; the other three eventually became well with conservative treatment, in two cases in spite of premature obliteration of the pleural space. They were left, however, with considerable pleural thickening and mediastinal shift, though neither complication led to symptoms or disability.

4. *Obliterative changes.* Thirteen of the original 54 pneumothoraces developed obliterative changes ultimately leading to expansion of the lung before it was desired. In six the changes were spontaneous, but only one of these had had a complete pneumothorax. In the other seven fluid in the space preceded, and was thought to have initiated, the process. Six of the 13 eventually relapsed.

5. *The 'frozen' lung.* The rigid inexpansible lung should properly be considered later, for its significance is seen above all at a time when treatment should have finished. There were seven patients in the series who showed this change to some extent. Six had had early atelectasis, permanently affecting the upper lobe in one case. Atelectasis is, indeed, often the start of a 'frozen' lung, so that refills are better not resumed until the lung has become aerated if it will. But a more potent factor is pleural effusion. All these seven patients had had fluid, which was cumulative in four cases and purulent in two of these. They were all left with a thickened pleura and mediastinal displacement. The surprising thing is that only one complained of symptoms from the complication.

6. *Rupture of adhesions.* This was met with only once, and affected an inadequate partial pneumothorax 14 months old. An acute effusion followed immediately, becoming later a tuberculous empyema.

7. *'Spontaneous' pneumothorax.* A spontaneous, or probably more correctly a traumatic, pneumothorax was recognized once—a surprisingly small incidence. It was followed for four months by a serous effusion, which then became absorbed without affecting subsequent treatment.

8. *Air embolism.* There was no clear example of this complication. One patient, whose pneumothorax was of eight years' duration, became faint during a refill, but the incident was regarded at the time as a minor vaso-vagal attack.

9. *Other complications.* One patient coughed a little blood a few times after refills, presumably from trauma by the needle, as the pneumothorax was partial and inadequate. There were no ill effects. Another patient had frequent short bouts of pyrexia after bilateral refills. They were never explained.

D. *Closure of Cavities*

Thirty-six patients had pulmonary cavities when their pneumothoraces were induced. One other developed a cavity three months after induction. His pneumothorax was inadequate and partial, and would have been given up had he agreed to a thoracoplasty. Of the total 37 cases, closure of the cavities was achieved in 31. Four required a supplementary phrenic nerve crush, and in 14 others division of adhesions was thought to be the determining factor. Atelectasis appeared to play no part, for the number of patients whose cavities closed was similar among those who never showed it (15 in 19) and among those who

did (16 in 17). Table V relates the incidence of cavity closure to the type of pneumothorax. Its significance is discussed later. In two-thirds of the cases the cavities closed within three months of establishing the final pneumothorax, but a few took several months, and one a year (Table VI).

Persistent cavitation. All the six patients in whom artificial pneumothorax failed to close the cavity or cavities had an inadequate partial pneumothorax. Two of this minority then had other treatment—one a thoracoplasty, and one

TABLE V

Closure of Cavities

	Number of cases with cavitation	*Number with cavity closure*
Complete A.P.	13	13 (Phrenic nerve crush in 1)
Adequate partial A.P.	4	4
Inadequate partial A.P.	20	14 (Phrenic nerve crush in 3)

TABLE VI

Type of A.P.	*Time of cavity closure in months*									
	1	2	3	4	5	6	7	8	11	12
Complete or adequate	6	5	1	..	..	1	1	2	1	..
Partial inadequate	5	..	3	1	2	..	1	..	1	1
All types	11	5	4	1	2	1	2	2	2	1

a pneumoperitoneum and phrenic nerve crush—additional to the pneumothorax. Both have kept well since. The remaining four died, two from tuberculous empyema, one from disease spreading to the other lung, and the fourth after a second-stage thoracoplasty.

E. *Duration of Institutional Treatment*

The average time of institutional treatment was 7·6 months after induction. Table VII gives the subsequent length of hospital and sanatorium treatment

TABLE VII

Type of A.P.	*Average stay in hospital after induction (months)*	*Average stay in sanatorium after induction (months)*	*Average total in-patient treatment after induction (months)*
Complete . .	2·7	3·9	6·6
Adequate partial .	4·1	4·1	7·8
Inadequate partial .	3·7	5·4	8·5

required by patients with the different types of pneumothorax. So many factors are involv d besides the type of pneumothorax that the differences between the groups cannot be regarded as important. The figures are given merely to show that the average length of institutional treatment in this series was similar to that found in the general run of patients.

F. *Premature Abandonment of Pneumothorax within Three Years*

We intended if possible to keep all the pneumothoraces for at least three and preferably five years, the latter period being regarded as desirable when there had initially been cavitation. But it was found impossible, or thought inadvisable, to continue nine of the 54 pneumothoraces even for three years. Three produced tuberculous empyemas, four spontaneous obliteration, and one was neglected by the patient. One other patient, with persisting cavitation, had a thoracoplasty, and has since kept well for four years. Of the three with tuberculous empyemas one had too much contralateral disease for surgical collapse to be attempted, but the other two were treated by thoracoplasty. One died after the second stage from spreading tuberculosis; the other is alive and well 10 years after a total thoracoplasty. Only one of the five patients whose pneumothoraces became obliterated in less than three years has remained well. Here the pneumothorax had been induced because of moderately extensive infiltration without obvious cavitation, and it had been effective for 18 months. Three patients relapsed within two years, and one as late as seven years, after obliteration.

G. *Assessment after Three Years*

1. *Clinical condition.* Forty-five of the 54 original pneumothoraces were maintained for at least three years. All but three of the patients were well at this time. Excepting these three, none had tubercle bacilli in the sputum, and 34 had no sputum. The three who were unwell had been deteriorating, and they eventually died. One never had closure of his cavity, and unfortunately refused alternative surgical treatment. The other two had steadily extending disease in the other lung, although that on the side of the pneumothorax was quiescent.

2. *Radiological condition.* Judged radiographically, the disease in the lung under collapse therapy was reduced in 44 of the 45 cases. Eleven already showed some calcification. The only patient whose disease increased on the treated side was the one whose cavity never closed, and who refused surgical treatment. The other lung was still normal in 17 cases, and unchanged in eight. In thirteen others contralateral disease had diminished, and in seven it had increased, during this three-year period. Extension of disease to a healthy opposite lung, when that in the lung on the pneumothorax side was thought to be controlled (albeit by an inadequate partial pneumothorax), happened only twice.

3. *Reopened cavities.* Of those whose pneumothorax was a going concern at three years, cavities had reopened within the first 18 months in four patients. One of them had needed a phrenic nerve crush initially to close the cavity, and its renewed patency coincided with the recovery of diaphragmatic function. The cavity closed again after a second operation. In another the lung had partially expanded and became adherent at the apex and to the lateral part of the chest wall. The other two showed no apparent cause for the reopening of their cavities. None of the four had had large cavities; three were small, and the other was 4 cm. in diameter. All four patients eventually closed their

cavities again, which then remained closed; but in three the closure took several months.

H. *Abandonment of Pneumothorax and Assessment after Expansion of the Lung*

Of the 45 pneumothoraces maintained for three years or longer, 12 are still continuing, and will be considered separately later. Twenty-six were abandoned intentionally, and seven were obliterated spontaneously before expansion was thought advisable.

1. *Intentional abandonment* (*26 cases*). In this group the pneumothoraces were kept for an average period of 5·3 years. In general, expansion of the lung was allowed rather earlier when the pneumothorax had been complete. At the termination of the pneumothorax 24 of the 26 patients were quite well. One of the remaining two had a recrudescent lesion in the other lung, and a pneumothorax was subsequently induced on that side. Her original disease was apparently healed. The other had bilateral disease, with tubercle bacilli in his sputum. He deteriorated steadily, having refused thoracoplasty on several occasions. Excluding this man, cavity closure and sputum conversion were still present in all these patients. The extent of disease in the treated lung had diminished in all but one, and 15 showed obvious calcification of the lesions. Two, however, had small encysted tuberculous empyemas. One other had an inexpansible 'frozen' lung with considerable mediastinal displacement. This condition caused discomfort, cough, and dyspnoea, which were relieved by phrenic paralysis. Thirteen of the 26 patients had had initial disease in the other lung. Only one, already mentioned, had any extension of this disease. Two others developed contralateral disease during treatment, although at the time their pneumothoraces had apparently been effective for two and four years respectively.

2. *Undesired obliteration* (*seven cases*). Because the pleural space was spontaneously obliterated seven pneumothoraces could not be kept for the full period, though each was effective for three years at least. Their average duration was 3·25 years, the longest lasting 4·3 years. All seven patients kept their cavities closed after expansion of the lung. The extent of disease was lessened in the recently collapsed lung, though calcification was evident in one case only. Six patients were quite well. The seventh was ill, thoracoplasty on the other side having failed to close a cavity there.

Follow-up after expansion of the lung. (1) *Intentional abandonment* (*26 cases*). At the last survey the patients in this group had been observed for periods up to seven years since their pneumothoraces were abandoned. The average period was two years. Two had died, one from relapse due to disease on the other side, for which further help was refused, and the other from intercurrent disease unrelated to his pulmonary tuberculosis, which was quiescent. Two others, both women, relapsed. One had a recrudescence with cavitation in the other lung a year after her pneumothorax was given up; the other relapsed, with freshly

active lesions in both lungs, three years after her pneumothorax was ended, and was found to have renal, ileocaecal, and pelvic tuberculosis in addition. Twenty-two patients had remained well and at work. Twenty-one of these had been followed for more than a year after termination of their pneumothoraces. Eighteen had no symptoms, and four had residual focal symptoms. None had tubercle bacilli in the sputum. Only one had had dyspnoea severe enough to interfere with ordinary exertion. This man, in middle life, was left with a good deal of pleural thickening and mediastinal shift, although he had not had either atelectasis or empyema. His dyspnoea and discomfort were both relieved by phrenic paralysis. Serial radiographs of the patients who remained well showed the old areas of disease to be unchanged or becoming more calcareous. Five had a persisting apical fluid cap, which was left alone. Considerable pleural thickening has remained in four, and mediastinal displacement in two. One of the two whose pneumothoraces had contained tuberculous pus when the pneumothorax was terminated absorbed it completely in four years, leaving pleural thickening; the other has had a lateral encysted collection of tuberculous pus for five years without apparent ill effect.

(2) *Undesired obliteration, but pneumothorax maintained for at least three years (seven cases).* The minimum follow-up of this small group was two years and three months, with an average of three and a half years. Five patients have remained well and free from symptoms with fibrotic and partly calcified old lesions. One has a long-standing atelectasis of the upper lobe, already present for seven years. The other two patients are dead. One had a tuberculous bronchopneumonia while overworking, two and a half years after expansion of the lung; the second had extensive cavitated disease in the other lung, which a thoracoplasty failed to arrest.

I. *Follow-up of Pneumothoraces Still Maintained*

Twelve patients still have their pneumothoraces, which are all more than five years old. Two have relapsed and are deteriorating because of recurrent active disease in the other lung, that on the pneumothorax side having remained quiescent, if not healed, for six and eight years respectively. The other 10 are well and working, and have had no relapses. Four have slight cough, with a trace of sputum free from tubercle bacilli. Most of these pneumothoraces have lasted five to seven years, the two longest 12 and 13 years. Both the latter are likely to be kept, for one patient has considerable pleural thickening and the other an atelectatic upper lobe dating from induction. One other patient, whose pneumothorax is nearly six years old, also has an inexpansible upper lobe, partly atelectatic. Seven of these 10 patients have had complete pneumothoraces, and only one shows basal obliterative changes. The other three have had adhesions all the time. Radiologically the lesions look fibrotic, and seven have calcification.

Termination of Pneumothorax in relation to Relapse

Table VIII shows the incidence of relapses in the four groups of patients. Whereas half (six in 12) of the patients in the first two groups, with premature

expansion and no alternative collapse therapy, relapsed, only four in 38 of the others did so. These figures may imply either that premature re-expansion of the lung and subsequent liability to relapse are merely unrelated expressions of a failure to control the disease, or that the former increases the risk of relapse. Whatever the explanation, the figures show that in this particular series the

TABLE VIII

Group	*Number of patients*	*Number with relapses*
1. Re-expansion in under 3 years (no alternative collapse therapy advised)	5	4 (3 within 2 years)
2. A.P. maintained for at least 3 years, but re-expansion earlier than desirable	7	2 (within 3 years)
3. Intentional abandonment	26	2 (within 3 years)
4. Pneumothorax still maintained	12	2

risk of later relapse was more than four times as great among patients whose pneumothoraces failed to run for their allotted span.

Return to Work

A principal aim of treatment has been to make the patients fit for work, if possible at their former employment. Only four failed to return to work. Of the other 46, 33 resumed their former pursuits. Thirteen did lighter jobs. The time taken to return to work varied widely, but averaged 15 months. Of those who eventually resumed work 88 per cent. did so within two years. At the last survey 38 of the 50 patients were fit and working. Six had died from the disease, and one other from an unrelated illness. The remaining five were in relapse.

Discussion

Many questions about treatment by pneumothorax were beyond the scope of the present investigation. How artificial pneumothorax compares with treatment by rest alone, or with other ways of relaxing and immobilizing an affected lung, or today with prolonged chemotherapy, are problems for a much more extensive and combined research. There is nothing of this kind in the literature, so that the comparative value of treatment by pneumothorax is still undemonstrated. In its practice this fact is often overlooked, a choice of treatment being made as though there was no lack of such evidence. The choice would be easier, and perhaps more reliable, if there were agreement about pneumothorax itself. This is not so at present, chiefly owing to the scarcity of reports on patients whose adhesions have been divided when possible as a matter of course, and whose supervision has been continuously in the same hands. Indeed, the literature of treatment by pneumothorax may be said to remain much where

it stood twenty years ago, although the practice has marched ahead. Against this background the present series of patients should be viewed. It largely covers the period of change, every facility was given for surgical help with adhesions, and treatment was under the same guidance throughout. The series thus fulfils the needs of a modern survey, except that the limited number prohibits statistical analysis. For this purpose we should have had to include most of the clinic population, not only the cases which we had followed completely. We chose the latter because they offered the advantages of a homogeneous series.

Besides this difficulty there was another which might well have affected the interpretation of the records. We refer to the effect of experience with the series upon our own policy of selection and management; for changes of policy would have led to errors when analysing the series as a whole. But in reviewing the series with this possibility in mind we were unable to find any differences which gave the later patients attributable benefit. Perhaps the best example was seen in the problem of when artificial pneumothorax should be begun. Few of the early patients, but many of the later ones, had much initial rest in bed; yet the incidence of complications was uniform and low. Those who had complications had more acute disease, and they were treated early in spite of the risks, because their prognosis was thought to be desperate otherwise. Apart from these cases our experience points to the fact that preliminary rest in bed need not be long. A few weeks are enough in which to judge initial powers of recovery, though even in this time 16 patients of the present series deteriorated while resting at home before admission to hospital. Early active treatment, moreover, often strengthens morale, and improvement with rest alone may be a deceptive argument for waiving a pneumothorax which is really needed. Most inductions will in any event be done after the disease has already existed for some time. The average time in our series was eight months from the onset of symptoms.

At induction most of the selected patients fulfilled certain criteria widely accepted as indicating suitability for pneumothorax treatment: constitutional symptoms were minimal, sputum was not copious, cavities were less than 5 cm. in diameter, and the disease was very rarely either pneumonic or fibrotic in type. But nearly all had extensive disease, which was bilateral in 30 cases. Only one had a minimal lesion (National Tuberculosis Association, 1940). Tuberculosis of major bronchi was not looked for as a routine until quite recently, so that its influence on treatment by pneumothorax cannot be judged from the present series. Radiological evidence pointing to disease in segmental bronchi was found in only five patients, all of whom had an eventful course. Our experience with lateral radiographs now suggests that tuberculous bronchitis may well have been present more often. Atelectasis of a segment or sub-segment as part of a tuberculous lesion may be compatible with a favourable result from artificial pneumothorax no less than from thoracoplasty, but most physicians are reluctant to embark upon pneumothorax treatment when this condition is found, and we agree with this view. Comparative investigation

is needed to decide whether pneumothorax should still have a place in the care of such patients.

The first, and in many ways the chief, technical problem of treatment by pneumothorax is the management of pleural adhesions. Adhesions were almost always found, and they were more extensive when the symptoms had included pain. Eleven of 13 patients with a history of pain or dry pleurisy had extensive adhesions. None of those with limited adhesions had had pain, and only one of those with adhesions of moderate extent. This relationship between pain and the finding of extensive pleural adhesion is important, deserving much more notice than it has yet had. Since it bears upon the extent of adhesion section likely to be required, it affects the immediate risks. When pain has been persistent, the probability of meeting indivisible or dangerous adhesions may even add weight to an argument for some form of treatment other than pneumothorax. When adhesions were extensive, partial rather than complete division was the rule (13 of 15 attempted; Table IV), chiefly because of the danger of severing adhesions to the superior mediastinum. Though complete division was rare (one case), so, too, was absolute failure (one case). Division was possible in 14 out of 15 patients in this group, and in 21 out of 22 of those with moderate or limited adhesions. Only 10 of all the 37 patients in whom division of adhesions was required or attempted needed more than one thoracoscopy, and only one patient needed more than two. A few patients came to serious or permanent harm after division of adhesions. There was one bronchopleural fistula with a haemothorax, which became a secondarily infected empyema. Seven other patients had progressing pleural effusions within a month, four of which became purulent later. Minor effusions were seen in six others; here the fluid was left alone, and was always absorbed within a few weeks.

One early event in treatment by pneumothorax, most often a sequel to division of adhesions, has led to some concern in recent years. This is the occurrence of atelectasis. Relatively common when the lung is freed completely, it usually occurs at once or within a few days, and is seldom caused by intrapleural tension. It happened in the present series after 15 of 44 operations for division of adhesions, and seven times soon after induction. It involved the entire lung on 14 occasions, and the affected lobe or segment alone in the other eight. At first we thought it might lead to chronic breathlessness and pleural effusions, with their remote perils, besides the risk of worsening any disease in the other lung. In the event not one of these hazards amounted to anything. Generally the lung became aerated rapidly, and in 14 cases refills were again required within a month. Only four patients retained the atelectasis permanently. One of them was found to have tuberculous bronchitis, and another rapidly developed a purulent effusion. Of the 22 patients with the complication these were the only two who came to any harm. We now regard atelectasis as a comparatively minor incident, unlikely to interfere with the success of treatment by pneumothorax, and often the best token of a 'free' lung and of the utmost immobilization and relaxation of the diseased area. Its commonness after prolonged division of extensive adhesions is perhaps a hint that this

operation is often causative, suggesting a reflex origin on a par with some examples of traumatic massive collapse of the lung. Most of our patients had at the time little sputum, which did not increase as the lung expanded, so that it is unlikely that retained secretion could have been solely responsible.

There is agreement already that pleural effusions are the chief complication of pneumothorax treatment. Fifteen of our 54 pneumothoraces collected small effusions, which usually came within a few weeks and remained for a few more, occasionally for as long as a few months. Two of them were recurrent. Such effusions, keeping below the level of the dome of the diaphragm, never became empyemas, and in only four of the 15 was the presence of fluid thought to have led to undesirable obliteration of the pneumothorax. Everything points to the harmlessness of these effusions. At the time they were not regarded as indicating a vulnerable pleura, and their subsequent history, and that of the pneumothoraces in which they were met, bore out this view. There was no reason to think that anything would have been gained by abandoning the treatment on their appearance. Larger cumulative effusions, however, have a very different fate. There were 15. Excepting one, they formed within two years, so that late effusions of this type were rare. They were commoner when indivisible adhesions were present; only four were found when the lung was completely free. Eight followed closely on division of adhesions, which in each case were considerable in extent. Four of the 15 became absorbed in a few months. Two others recurred, but did no harm. The remaining nine persisted, eight becoming tuberculous empyemas; four of these patients survived and in the long run did well (three treated conservatively), although obliteration of the pneumothorax was premature in two of them, fortunately without reopened cavities. The other four eventually died from extending disease in the other lung. With the present series, therefore, our experience of the menace of large pleural effusions agrees with that of others. The joint effects of atelectasis and pleural fluid go far to account for the complication of 'frozen' lung, as the few figures in the analysis suggest. Here it was not a serious matter, though it is so when respiratory reserve is already low, and may be so if the lung becomes infected by pyogenic organisms, which is fortunately rare. Neither these risks nor the presence of symptoms is the chief bane of a 'frozen' lung, but the alternatives of continuing refills indefinitely, accepting the risks of major surgery, or chancing the hazards of a pleural void. Our next concern to fluid was obliteration of the pleural space. Thirteen of the 54 cases had fluid which led on to premature expansion of the lung. This event either followed fluid, or occurred in the presence of an incomplete pneumothorax. The long-term effect upon prognosis was seen at subsequent relapses in six of the 13 patients, compared with four who relapsed out of 38 after five years or more of pneumothorax treatment.

The figures in the analysis show that the results justified to the patients their prolonged treatment. By the first three months only a few were left with symptoms and tubercle bacilli in their sputum (seven in 34); most of these patients belonged to the small group whose disease was more acute than usual in the series. Forty-five of the pneumothoraces were still under way at the end

of the third year. All but three of these patients were well, and had no tubercle bacilli in their sputum, or no sputum at all. The extent of disease on the treated side was lessened, and 11 already had calcification. Thirty-one out of 37 cavities were closed, 14 after division of adhesions, and four with the added help of a single phrenic nerve crush. In five out of seven cases in which contralateral disease had increased, this increase happened early, before the disease on the side of the pneumothorax had been controlled.

Most recent opinion has regarded a 'free' lung as a paramount necessity for successful treatment by pneumothorax, and in particular for the closure of cavities. Whatever the reasons—and much that has been written on this subject is chiefly speculation—there is in practice a close relation between the freedom of relaxation of the lung in and around a diseased area and the probability that cavities will close. No patient in the present series who achieved a complete or adequate partial pneumothorax subsequently failed to close a cavity (Table V). But six out of 20 failed to do so among those who had cavities in upper lobes adherent to the mediastinum, and whose pneumothoraces were consequently regarded as inadequate but were continued. In the latter group, however, there was still a majority whose cavities closed without undue delay (Table VI), and without any eventual difference in the permanence of the result and fitness of the patients in comparison with others whose pneumothoraces were technically better. They probably owe this result to the fact that lateral and antero-posterior relaxation of the lung, a situation like that of the old-fashioned thoracoplasty, is in them enough for the purpose. The main defect is that the lung fails to relax vertically, bringing the apex of the upper lobe into a more dependent position. Such pneumothoraces, although imperfect, may evidently play a part in healing the disease. They should be judged on the merit of their achievement before they are discarded in favour of surgical treatment. Patients with indivisible adhesions—apart from adhesions to the superior mediastinum—preventing proper relaxation of diseased lung, were treated in some other way, and are not included in this paper, since artificial pneumothorax was not their definitive treatment.

Another important technical problem centres on the time required for closure of cavities. Two-thirds of the cases required less than three months; but a few took several months longer (Table VI), and their cavities would not have closed at all without a patient effort by frequent and adequate refills. These examples show the importance of persevering, at any rate well beyond three months, before concluding that a pneumothorax will fail to close a cavity. Our experience has made us reluctant to decide earlier. There was a small number of patients (four in 37) in whom a cavity reopened while the pneumothorax was maintained. One of these needed a phrenic nerve crush, and all four needed additional refills, though previous refills were mistakenly thought to have been adequate. The cavities then closed again, and all the four patients did well. These events show the need of a constant watch for the reappearance of cavitation formerly known to have been present. Once the collapse of the lung has been established sufficiently to keep any cavity closed, expansion of a diseased lobe beyond

this extent during treatment implies a failing pneumothorax or a faulty technique.

We have seen that by the end of the third year of treatment most patients were well, and their disease was quiescent. This result was maintained at the time the pneumothorax treatment ceased. Of 26 patients whose pneumothoraces were abandoned intentionally after an average duration of 5·3 years, 24 were well at that time, and 25 had their cavities closed and their sputum free from tubercle bacilli. Six out of seven others whose pneumothoraces were obliterated spontaneously after an average duration of 3·25 years were also well, and all seven had kept their original cavities closed. At the last survey 22 of the former group and five of the latter remained well, as well as 10 of the 12 whose pneumothoraces were still maintained. Those who relapsed did so owing to the reactivation of lesions already present in the opposite lung, at least as frequently as from disease on the treated side.

The ability to resume and to remain at work is really the best test of treatment by pneumothorax. Judged by this test the treatment stands well in this series, especially if the kind of disease we were dealing with—frequently bilateral and with cavities, and almost always fairly extensive—is borne in mind. Less than one patient in 10 failed to resume work of any kind, and two-thirds resumed their former occupations. Thirty-eight of the 50 patients were fit and working at the last survey. These figures also help to show how far pneumothorax treatment may itself entail disability by interference with respiratory exchange. Capacity for former work implies a fair response to physiological tests, and includes much more. Here we reach the point of asking how far the observations in the present paper go towards a better understanding of the conditions for success with pneumothorax treatment. They were not designed as a controlled experiment: therefore they go no farther than to give results in a group of patients whose treatment was conducted in a certain way. We have seen that these results were good, and it seems fair to regard the more important decisions on matters of policy in the present series as those which decide the success or failure of treatment by pneumothorax. The first is that, in abiding by accepted contra-indications to its use, we chose a series of patients who did well. A second point is that adhesions were always divided early when it was safe to do so, to give the lung free relaxation; and only those pneumothoraces were kept which were complete, or had adhesions remote from the diseased areas or limited to the superior mediastinum. There was also a minimum duration of three years, preferably five years in the presence of initial cavitation, and a single control of policy throughout.

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Summary

A survey is given of the present situation of artificial pneumothorax as a treatment for pulmonary tuberculosis. With few exceptions the recorded series are devoid of uniform assessment and long continuity of supervision, because they are compiled from the work of numerous observers. Moreover, they deal mostly with patients whose pleural adhesions were not divided, so that many had unsatisfactory pneumothoraces.

The present paper concerns the treatment by pneumothorax of 50 patients who were under the same supervision continuously, and whose pleural adhesions were divided at an early stage of treatment whenever possible. Fifty-four pneumothoraces (four bilateral) were induced between 1935 and 1944, and the patients were observed until 1949, that is for periods of five to 15 years. Eighteen pneumothoraces were done for active infiltration, and 36 for infiltration with cavitation. Severe toxaemia, pneumonic disease, predominant fibrosis, atelectasis, and very large cavities were all regarded as contra-indications to this form of treatment. A few patients with one or other of these features were included early in the series, but they failed to benefit, or were harmed.

Atelectasis of the lung, or of a lobe, was a common early complication (22 in 54 pneumothoraces), chiefly after thoracoscopic division of adhesions (15 in 22). With only two exceptions it was unimportant. The lung was aerated quickly again in all but four cases. Pleural effusion, the main complication (30 cases in 54), did not chiefly affect patients who had little preliminary rest. Small effusions, not rising above the dome of the diaphragm, were benign apart from a little risk (four cases in 15) that obliteration of the pleural space might follow. Large effusions were equally common, were often persistent, and in eight out of 15 cases followed division of extensive adhesions. Tuberculous empyema and premature loss of the pneumothorax were the chief risks. A pneumothorax with extensive adhesions, whether these were divisible or not, had a greater risk of effusion and of an effusion becoming purulent.

The pneumothoraces were classified as (1) 'complete', when free from pleural adhesions; (2) 'adequate partial', when adhesions were thought not to prevent relaxation of the diseased area; and (3) 'inadequate partial', when adhesions interfered with relaxation of the diseased area. Seventeen patients with pulmonary cavitation had pneumothoraces of the first two types, and in all of them the cavities closed. Twenty others with cavitation had pneumothoraces of the third type; in 14 of these the cavities closed, aided by phrenic nerve paralysis in three.

Nine of the 54 pneumothoraces were abandoned for various reasons, or obliterated, within three years. Only one of these patients remained well without further treatment. Undesired obliteration occurred in seven others after more than three years; five of these patients remained well. Twenty-six pneumothoraces were deliberately abandoned after an average duration of 5·3 years. Twenty-two of these patients remained well. Twelve patients still have pneumothoraces of more than five years' duration; all have quiescent

disease in the treated lung. Thirty-eight of the original 50 patients are well and at work. Of the remainder six have died from their disease, one has died from an unrelated illness, and five are in relapse.

Our experience with this series of patients during 15 years favours the use of artificial pneumothorax. We think the chief conditions for success have been: recognition of certain contra-indications; early division of pleural adhesions; maintenance of those pneumothoraces only which were complete, or had adhesions remote from the diseased area or limited to the superior mediastinum; and a minimum duration of three years, and preferably five years in the presence of initial cavitation. Less tangible, but equally important, is a single control of policy throughout treatment.

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THE HEREDITY OF HYPERTENSION IN DIABETES MELLITUS[1]

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It is well known that hypertension and arteriosclerosis are commonly met with in diabetics over the age of 50 years. Exactly why this is so is not clear, but the view is generally accepted that diabetes contributes in some way to the development of arterial degeneration. It is now recognized that heredity is an important aetiological factor in essential hypertension and the arterial changes which accompany it. The present paper is an attempt to evaluate the part played by heredity in causing the hypertension which occurs in diabetic subjects.

The Heredity of Essential Hypertension

In approaching the problem it is first necessary to summarize the present state of our knowledge of heredity in essential hypertension, so that its behaviour may be compared with that occurring in diabetes. Long before Mendelian laws were formulated, clinicians recognized that the ills associated with high blood-pressure and arterial disease tended to afflict certain families. In 1876 Dieulafoy reported that heredity was a more important factor in cerebral haemorrhage than in phthisis. He therefore advised that people with such a family history should not be accepted for insurance. Raymond (1907) and Ayman (1933) described families which illustrated the point in question. These and many other isolated observations pointed to the conclusion that hypertension was inherited and transmitted as a Mendelian dominant; more comprehensive studies designed to prove this hypothesis then followed, one of the earliest being that of Weitz (1923). Weitz extracted careful histories from 82 hypertensive patients, and from a group of unselected patients who acted as controls. He found definite evidence of hypertension in the relatives of 63 (76·8 per cent.) of the hypertensive patients, but in only 30·3 per cent. of the controls. He also noted the occurrence of hypertension in three successive generations, and pointed out that this was strong evidence that it was a true dominant characteristic. Further, no familial tendency to hypertension was found in cases of nephritis, and he suggested that the family history should therefore be of considerable value in the differentiation between essential and renal hypertension. Ayman (1934) recorded the blood-pressure in the relatives who were visiting patients in hospital. Excluding those patients whose blood-pressures might have been altered by nephritis, aortic incompetence, severe illness, or other complicating factors, he chose 277 who were suitable for his investigation, and was able to

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record the blood-pressure in 1,524 of their relatives. Analysing his figures, he found that where both parents were normal 3·1 per cent. of the offspring had hypertension, that where one parent had hypertension, so did 28·3 per cent. of the offspring, and that where both parents were hypertensive the incidence of hypertension in their offspring rose to 45·5 per cent. Hines (1937) made a similar study, but also employed the cold pressor test. The value of this test was clearly demonstrated, for he found a familial tendency to hypertension to be five times as common amongst hyperreactors as amongst non-reactors, and he found no single hyperreactor whose parents were themselves neither hypertensive nor hyperreactive. He examined seven sets of identical twins, and found that the reactions of each pair to the test were identical, as opposed to three sets of fraternal twins, in two of which the reactions were dissimilar. As a result of studying a large number of relatives—57 in one case—he found that where both parents had normal blood-pressure and normal responses to the test all the children were normal. Where both parents were hypertensive or hyperreactors, 95 per cent. of the children were also either hypertensive or hyperreactors. Where only one parent was affected, abnormality was found in 43·4 per cent. of the children. These figures are strikingly close to the proportions which would be expected on the supposition that essential hypertension is transmitted as a Mendelian dominant characteristic, and do not seem compatible with any other simple explanation. Platt (1947, 1948), in a study of the heredity of hypertension, set out to examine the 'attractive possibility . . . that the cases without a family history are not essential hypertension'. His results are important, for he first confirmed the dominant nature of essential hypertension from a study of family histories. He then showed that there was no such hereditary influence where hypertension was secondary to other disorders such as nephritis. He thus emphasized the suggestion, originally made by Weitz (1923), that an important point in the differentiation between primary and secondary hypertension lies in the study of the family history. The present study of the heredity of hypertension in diabetes is based on Platt's methods.

The Blood-pressure in Diabetes

It is certain that diabetics tend to show hypertension and atheroma more than non-diabetics. Actual surveys of diabetic and non-diabetic patients have been made on numerous occasions, and in general it has been found that the blood-pressure tends to be higher among diabetics. Thus Marañon (1922) found the incidence of hypertension to be higher at all ages in the diabetic group; the blood-pressure was over 180 mm. Hg in 42 of 78 diabetics over the age of 40 years. Similar results were obtained by Hitzenberger and Richter-Quittner (1921), Kylin (1923), Koopman (1924), and Klein (1924). Major (1929) set out to compare the blood-pressure in a series of 408 diabetics over the age of 35 years with that found in a group of dispensary patients, in a group of hospital patients, and in a group of normal people largely drawn from the relatives and friends of the hospital patients. He divided the groups by age into quinquennia, and found that the curves obtained by plotting the mean systolic pressure

against age were very similar in the groups of diabetics and of hospital and dispensary patients, and that in all three the blood-pressure was considerably higher than in the group of normal subjects. There was, however, a slightly higher incidence of hypertension in the diabetic than in the other groups. Bell and Clawson (1928), in an account of the morbid anatomy of hypertension, found that 17 out of 40 diabetic patients who died over the age of 50 years had definite evidence of hypertension, and they calculated that hypertension was 2·7 times as frequent in diabetics as in non-diabetics at that age, though it was relatively infrequent under the age of 40 years. They found that only 5·5 per cent. of hypertensive persons over the age of 50 years had diabetes—a figure which is reasonably close to Janeway's (1913) 7·2 per cent.—and concluded that 'diabetes, therefore, appears to be at least a contributory cause in cases of arteriosclerosis and hypertension'. With respect to atheroma, it is not possible as in the case of blood-pressure to measure its extent in any patient, but clinical experience shows, and Joslin (1946) and his school have insisted, that diabetics are peculiarly prone to its development. In particular diabetics show an excessive incidence of coronary sclerosis and thrombosis, and of arterial degeneration in the legs and feet. This point has been frequently discussed in the literature (Wilder, 1926; Blotner, 1930; Nathanson, 1932; Enklewitz, 1934; Rabinowitch, 1935; Dolger, 1946).

The Relationship between Diabetes and Hypertension

It is apparent that diabetes is associated with a high incidence both of hypertension and of atheroma, but the reasons for the association are not known. The frequency of association of two events, however regular, cannot itself prove that either is the cause of the other. It is theoretically possible that hypertension causes diabetes, that diabetes causes hypertension, that both are simultaneously caused by the same agency, and that both coexist as separate diseases, there being some indirect reason for their frequent occurrence together. In an attempt to find other contributory causes for hypertension in diabetes, attention has been drawn to two main types of renal disease to which diabetics are liable. 1. *Intercapillary glomerulosclerosis* was first described by Kimmelstiel and Wilson (1936) from the post-mortem study of eight patients who had had diabetes for many years, terminating in severe oedema with gross albuminuria, hypertension, and renal failure. It seemed possible that the lesion they discovered might, in some cases at least, be the cause of hypertension in diabetes. Intercapillary glomerulosclerosis was at first definitely associated with the striking clinical syndrome just described (Anson, 1938; Derow, Altschule, and Schlesinger, 1939; Newburger and Peters, 1939; Herbut, 1941; Porter and Walker, 1941; Mauser, Rowe, and Michael, 1942), but has since been shown to be a characteristic finding in diabetes irrespective of hypertension (Allen, 1941; Siegel and Allen, 1941; Laipply, Eitzen, and Dutra, 1944; Bell, 1946). 2. The frequency of *chronic pyelonephritis* in diabetes has been emphasized by Bowen and Kutzman (1942). Eighty-four women with well-controlled diabetes were carefully examined for evidence of lesions of the urinary

tract, and only seven were passed as completely normal. Fifty-one of them had lesions in the upper urinary tract, the most frequent being pyelitis, and 34 of these 51 patients were hypertensive, with a marked degree of retinal arteriosclerosis. Twenty-six had lesions in the lower urinary tract only, and of these only 13 were hypertensive. It was suggested that mild chronic urinary infection was exceedingly common in female diabetics and easily overlooked owing to preoccupation with the diabetes, but that where infection ascended into the upper urinary tract and led to pyelonephritis, damage to the kidney might result in hypertension.

It was suggested by Härle (1921) that hypertension might be the cause of diabetes. He examined a few cases of hypertension with great care, having first excluded all other factors which it was thought might affect the blood-sugar, and, having withheld such drugs as caffeine, he concluded that even in uncomplicated hypertension hyperglycaemia was not infrequently present. The clinical implications of hyperglycaemia in hypertension were taken up by Marañon (1922). Finding that the incidence of hypertension was higher at all ages in diabetics than in non-diabetics, he was particularly struck by the frequency with which hypertension preceded glycosuria. He labelled such cases 'pre-diabetic', and in a number of them was able to observe typical diabetes slowly developing. He found, as had previous authors, that though hyperglycaemia was unusually common in hypertension its severity was not proportional to the height of the blood-pressure (O'Hare, 1920; Hitzenberger and Richter-Quittner, 1921). Yet even in some patients with a normal fasting blood-sugar hyperglycaemia and glycosuria were provoked by a glucose-tolerance test. Marañon concluded that hypertension was a pre-diabetic condition, and traced three stages in its natural history: first, hypertension with lowered glucose-tolerance and occasional glycosuria; secondly, permanent hyperglycaemia and mild diabetes; and finally, severe diabetes with a lowering of the blood-pressure. This interesting clinical study appears to be the only published work to provide a reasonable argument that hypertension leads to diabetes. It does not prove any causal relation between the two diseases, nor does it set out to do so, but it provides a fresh point of view as to their relationship. Kramer (1928) approached the problem from a different angle. He pointed out that both hypertension and diabetes were diseases particularly of the sixth decade, that the distribution of hypertension in the different age-groups was much the same in diabetics and in non-diabetics, and that both diseases were chiefly caused by the same factors of diet, mental unrest, endocrine disorder, infections, and heredity. He argued that where these causes were operating both diseases might arise, and that diabetes would be particularly liable to supervene on hypertension if the individual were already predisposed to it by reason of heredity or race. Sherrill (1933) argued that hypertension and diabetes were both predominantly diseases of the sixth decade, and were therefore to be expected to occur together frequently, and he explained the excessive frequency of hypertension in diabetics (35 per cent. of patients over 20 years old in his series) on the basis of their tendency to develop arterial disease and obesity.

Allowing for these factors, he could find no evidence that diabetes was a specific and direct factor in increasing arterial pressure. The close relationship of these conditions with obesity was clearly shown by Musser and Wright (1933). They found that hypertension was far commoner among obese diabetics, and impaired glucose-tolerance among obese hypertensives. As Mohler (1925) had previously shown, dieting led to improvement in both diabetes and blood-pressure, and it was inferred by these authors that hypertension occurring in diabetes was due not to the diabetes but to obesity.

The most convincing evidence that diabetes is directly or indirectly the cause of arterial degeneration and hypertension is obtained from studies of juvenile diabetics who have been treated with insulin for many years. Thus White and Waskow (1948) showed that of 220 juvenile diabetics who had had the disease for more than 20 years, 203 (92 per cent.) had demonstrable vascular disease, and 120 (55 per cent.) had hypertension. By the age of 29 years 60 per cent. showed retinal sclerosis, 50 per cent. retinal haemorrhage, 50 per cent. calcified arteries, and 30 per cent. nephritis. A point of particular importance is that these changes occurred in the third decade, an age-group in which they are rarely met with in non-diabetics. The authors emphasized the fact that the treatment of these patients in their early years was, by modern standards, inadequate. That efficiency of control may be a factor in preventing cardiovascular degeneration is suggested by the observation that diabetic coma occurred in only 10 per cent. of those unaffected, in 40 per cent. of those moderately affected, and in 60 per cent. of those incapacitated, by vascular disease. In the same paper the authors suggested that the inheritance of a poor vascular system is a possible aetiological factor, and mentioned the case of similar twins (Cases 4768 and 6208 in their series) who developed similar vascular lesions, calcified arteries, retinitis proliferans, and nephritis, and suffered cardiorenal deaths, almost at the same times. Ricketts (1948) wrote: 'Heredity is generally conceded to be an important cause of diabetes. It undoubtedly plays a role in some cases of vascular disease in which diabetes is not present, but whether inherited tendencies to both diabetes and vascular disease occur in the same individual cannot be established by available data.' He concluded that vascular disease in diabetes is the result, not the cause or parallel concomitant, of diabetes, and that the most reasonable conjecture was that long-continued poor control of blood-sugar, or lipoids, or both, would prove to be at least one of the factors involved. Root (1948) compared the incidence of non-diabetic cardiovascular deaths, in people over 45 years old during the year 1945, according to figures from the Metropolitan Life Assurance Company, with the incidence of cardiovascular deaths among 1,500 diabetics investigated at the Deaconess Hospital from 1944 to 1948. Cardiovascular disease caused 70 per cent. of the diabetic deaths and 60·5 per cent. of the non-diabetic deaths. These figures suggest that in people over 45 the difference in this respect between diabetics and non-diabetics is not impressive. Root also emphasized the importance of the observation that premature arteriosclerosis occurs outside the normal age-group in diabetics who have had the disease for more than 15 years.

Dolger (1947) found that of 200 patients with diabetes who had been under careful observation for 25 years none escaped retinopathy, regardless of the age of onset, severity of diabetes, or method of treatment. Fifty per cent. already had hypertension at the time when retinopathy was detected. Lawrence (1949) discussed the possibility that hyperglycaemia might be the primary and direct cause of arteriosclerotic complications in diabetes. He considered that on the whole the worst-controlled cases of hyperglycaemia develop vascular complications earlier and more often, but did not know how poor control contributes to vascular change. He also said: 'The innately different quality of vascular resistance must play a part in diabetic as well as other types of vascular degeneration. One sees a similar state of blood vessels at 40 and 85.'

The Heredity of Hypertension in Diabetes

It is apparent from this short review that any method of identifying essential hypertension, whether it occurs alone or in association with other disease, would be helpful in disentangling the complex 'hypertensive diabetes'. Such a method was provided by Platt (1947) who showed that if patients with essential hypertension were carefully questioned as to indications of hypertensive disease in their family history, a high proportion would give a positive and a low proportion a definitely negative family history, and that the remainder would give histories either vaguely suggestive of hypertension or useless owing to insufficient evidence. This result was due to the nature of essential hypertension as a Mendelian dominant characteristic. The normal population showed a lower proportion of positive and a higher proportion of negative family histories. Patients with secondary hypertension due, for example, to renal disease closely resembled the normal population in this respect. In applying this method Platt pointed out that, as evidence of a hypertensive family history: 'We have often to be content with the patient's statement that the parent died of heart failure, dropsy (presumably cardiac), seizure, stroke, apoplexy, or Bright's disease. Since the majority of cases of hypertension succumb to heart failure rather than to cerebral haemorrhage or uraemia, a history of death from cardiac disease must be considered important. Such evidence could not be deemed acceptable if it occurred only in a moderate number of histories, especially having regard to the frequency of hypertension in later life, but if we are dealing with a dominant Mendelian character the history should be obtainable from one or both parents of practically every case, and if this were so it would indeed be convincing.' Family histories with respect to hypertension in the present series of diabetic patients have therefore been treated in the manner described by Platt, and the patients have been divided into four groups. Group I comprises cases in which the evidence of hypertension in one or both parents is strong or, if uncertain, is supported by a history suggestive of hypertensive disease in siblings of the parents or of the patient. Group II comprises cases in which the evidence points only to a reasonable probability of hypertensive disease in at least one parent or sibling. Group III comprises cases in which the evidence is lacking—for instance, when nothing is known of the cause

of death of a parent, or when the parent died from some cause other than hypertension at an early age (younger than the present age of the patient). These cases neither support nor refute the hypothesis. Group IV comprises cases in which the evidence is against hypertensive disease in parents or in siblings. It is obvious that by this method gross errors in interpretation of the family history may arise in individual cases. Thus a 'stroke' may be due to embolism in a patient with normal blood-pressure, and perfectly good health may be enjoyed by the very aged in spite of a remarkably high pressure (Howell, 1942). Errors also arise from the fact that death in hypertension is commonly brought about by atheroma, and atheroma and hypertension are not the same. Extensive atheroma may exist without hypertension, and furthermore may be severe in one group of vessels, such as the coronary or cerebral, and mild or absent elsewhere. In young patients, moreover, gross hypertension occasionally exists for long periods without the development of significant atheroma. Nevertheless it appears that on the whole chronic hypertension aggravates or hastens the development of atheroma, and that deaths from cerebral vascular accidents or from coronary arterial disease usually indicate antecedent hypertension. It is rare for cerebral haemorrhage to occur in non-hypertensive subjects, and Cassidy (1946) estimated that about 70 per cent. of patients with coronary thrombosis had previously had hypertension. If, therefore, a sufficiently large number of patients is collected, evidence of the kind proposed is of statistical significance, even though the assessment of isolated cases is open to criticism. On the other hand, individual subjects will be met with whose survival in good health to the age of 70 years or over is wrongly taken to indicate normal blood-pressure. Here again, if a sufficiently large number of patients is collected, a significant statistical conclusion is possible. In the paper already referred to Platt showed that this was in fact the case.

Methods

Two hundred and nine diabetics over the age of 30 years have been studied. They were all attending the Diabetic Clinic in charge of one of us (L. C.) at Addenbrooke's Hospital, and most had been under his personal and regular supervision there for periods up to 23 years, or since their disease had been diagnosed. They were again examined at varying intervals between 1947 and 1949. They were unselected in the sense that all diabetics are encouraged to attend regularly for supervision every few months, and their surroundings were quite familiar to them. Patients whose diabetes was associated with such conditions as Cushing's syndrome, acromegaly, hyperthyroidism, nephritis, pyelitis, and haemochromatosis, which in themselves cause hypertension, have been excluded from the study. Diabetes itself may have been the cause of the 'hypertensive' family histories of four hypertensive diabetics and of one diabetic with a normal blood-pressure. The age and sex incidence are given in Table I. One hundred non-diabetic cases were collected by one of us (H. W. B.) from the wards and out-patient departments of St. Bartholomew's Hospital; 50 patients with essential hypertension and 50 without hypertension were

chosen. The majority of those with hypertension were attending the hospital hypertensive clinic under the direction of Dr. Geoffrey Evans, the rest being encountered in the course of routine work. Blood-pressures were measured in the out-patient department with the patient sitting down. The great majority were measured on more than one visit, and on each occasion the final result was based on at least three readings. The patients were all familiar with the clinic, and had been at rest some little time before examination. The problem as to what figure should be chosen as marking the dividing line between hyperten-

TABLE I

Incidence of Hypertension in Diabetics in Successive Decades of Age

Age-group (years)	*Number of patients*	*Not hypertensive*	*Hypertensive*	
			number	*%*
Men:				
30–39	8	5	3	37
40–49	15	13	2	13
50–59	19	13	6	31
60–69	21	10	11	52
70+	14	5	9	64
Total	77	46	31	
Women:				
30–39	5	2	3	60
40–49	14	7	7	50
50–59	34	10	24	70
60–69	56	15	41	73
70+	23	4	19	83
Total	132	38	94	
Men and women:				
30–39	13	7	6	46
40–49	29	20	9	31
50–59	53	23	30	57
60–69	77	25	52	67
70+	37	9	28	76
Total	209	84	125	

Summary: Total diabetics . . 209

Hypertensive diabetics (60% of total) 125 — men 31 — 15% of total diabetics; 40% of male diabetics

Hypertensive diabetics (60% of total) 125 — women 94 — 45% of total diabetics; 71% of female diabetics

sives and normals was a difficult one, and the final decision had to be arbitrary. It was clear that, whatever figure was taken, there would be certain borderline cases which would be difficult to assess accurately. In practice such cases were found to be relatively few, and do not significantly affect the final figures. Paul White (1945) gave the upper limit of the normal range as 150 mm. Hg systolic and 95 diastolic, and Lewis (1948) asserted that 'values that are above 160 mm. Hg definitely surpass normal limits'. On the other hand Robinson and Brucer (1939) gave statistical evidence that ideally the systolic pressure should be not higher than 90 to 130 and the diastolic not higher than 60 to 80 in either sex at any age. After carefully considering the evidence we have taken the

figure of 160 mm. Hg, recorded under the conditions described, as indicating systolic and 95 mm. Hg as indicating diastolic hypertension. The two are of different significance, but where either is present the patient has been placed

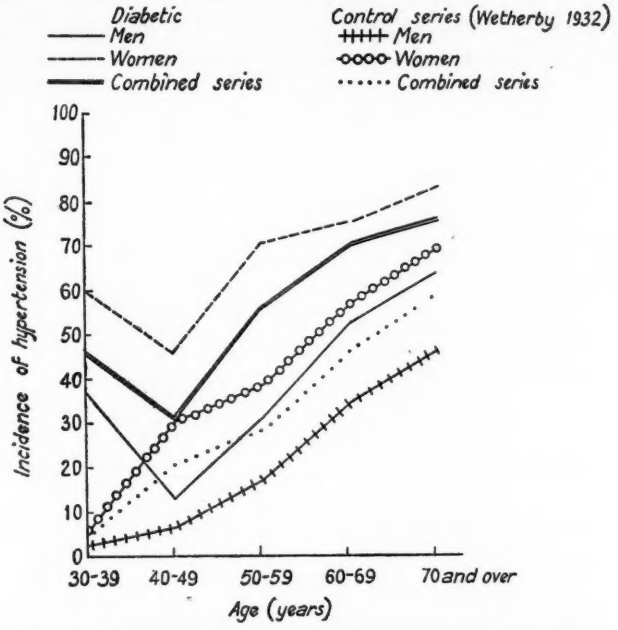

FIG. 1. Incidence of hypertension in diabetics in successive decades of age.

in the single category of hypertension. No attempt has been made to distinguish hypertension with a high diastolic pressure in the younger age-groups from the

TABLE II

Family History of Hypertension

For Group classification, see text

	Group I			Group II			Group III			Group IV		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
Hypertensive subjects:												
125 diabetics	12	34	46 (37%)	2	13	15 (12%)	11	35	46 (37%)	6	12	18 (14%)
50 controls	4	21	25 (50%)	4	6	10 (20%)	4	8	12 (24%)	2	1	3 (6%)
Non-hypertensive subjects:												
84 diabetics	9	10	19 (23%)	3	4	7 (8%)	12	7	19 (23%)	22	17	39 (46%)
50 controls	2	5	7 (14%)	3	1	4 (8%)	12	9	21 (42%)	12	6	18 (36%)

high systolic pressure with a relatively low diastolic pressure which is common in the aged.

Results

On the above basis 125 of the 209 diabetic patients were hypertensive and 84 were not. A far greater proportion of women than of men were hypertensive

—94 out of 132 women (71 per cent.) compared with 31 out of 77 men (40 per cent.) (Table I). In Table II the 125 hypertensive diabetics, the 84 non-hypertensive diabetics, and the 50 hypertensive and 50 non-hypertensive controls have been analysed according to the family history each gave of hypertension. The table shows that a 'positive' history of hypertension in the family was found in 46 of 125 (37 per cent.) hypertensive diabetics and in 50 per

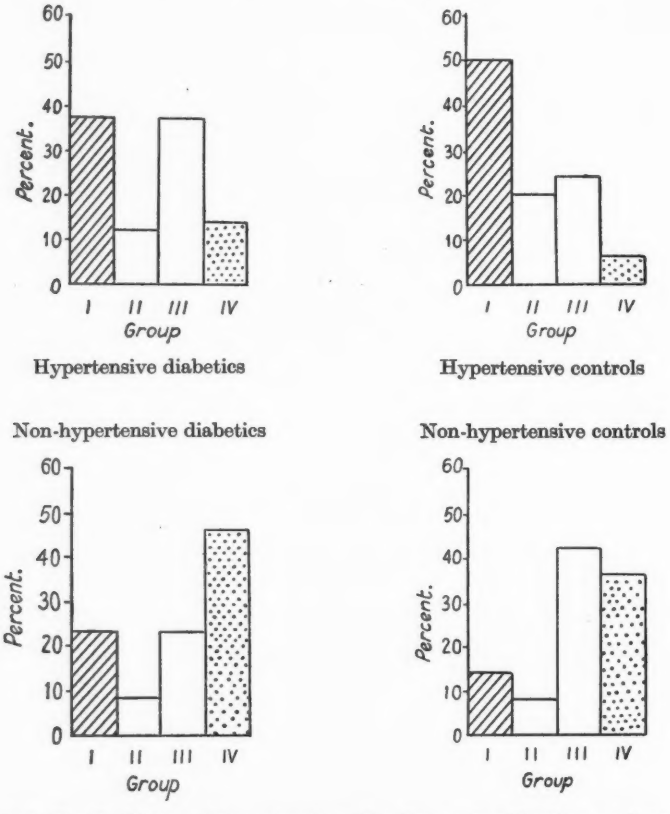

FIG. 2. Family history of hypertension. For Group classification, see text.

cent. of the hypertensive controls, as opposed to 19 of 84 non-hypertensive diabetics (23 per cent.) and 14 per cent. of non-hypertensive controls; a 'negative' family history of hypertension was found in 18 of 125 hypertensive diabetics (14 per cent.) and in 6 per cent. of hypertensive controls, as opposed to 39 of 84 non-hypertensive diabetics (46 per cent.) and 36 per cent. of non-hypertensive controls. These data are expressed graphically in Fig. 2. It will be remembered that Groups II and III contain the cases in which family histories are least definite, and it will be seen from Table II that Groups II and III together constitute 49 per cent. of the hypertensive and 31 per cent. of the non-hypertensive diabetics, compared with 44 per cent. of hypertensive and

TABLE III

Family History of Hypertension, omitting Groups II and III

	Group I	*Group IV*
Hypertensive subjects:		
64 diabetics . . .	46 (72%)	18 (28%)
28 controls . . .	25 (89%)	3 (11%)
Non-hypertensive subjects:		
58 diabetics . . .	19 (33%)	39 (67%)
25 controls . . .	7 (28%)	18 (72%)

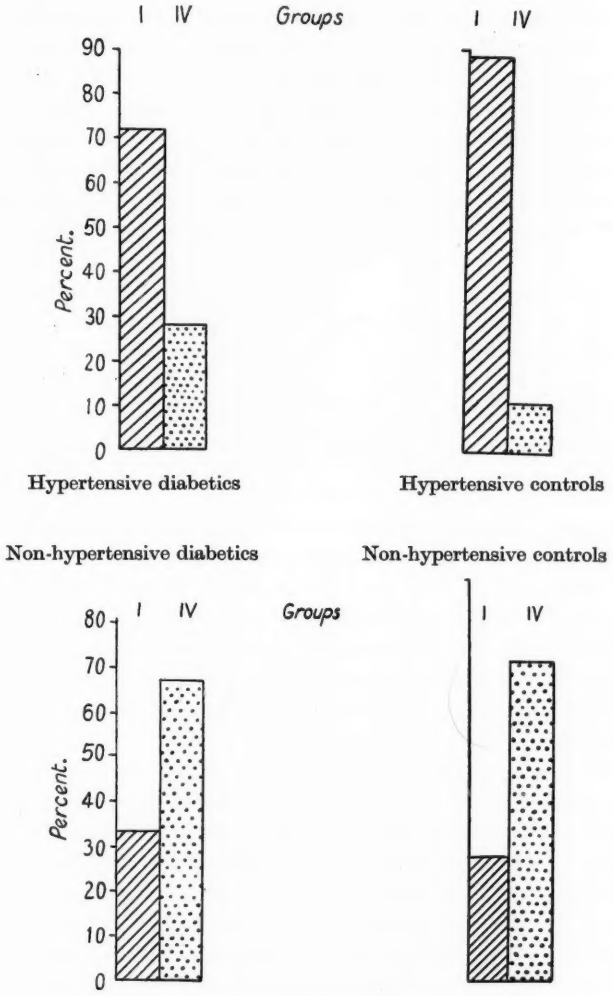

FIG. 3. Family history of hypertension, omitting Groups II and III.

50 per cent. of non-hypertensive controls. If Groups II and III are omitted, although some distortion of the analysis will occur, the differences between Groups I and IV show more clearly (Table III). Forty-six of 64 hypertensive diabetics (72 per cent.) and 89 per cent. of 28 hypertensive controls showed a positive family history of hypertension, as opposed to 19 of 58 non-hypertensive diabetics (33 per cent.) and 28 per cent. of non-hypertensive controls. On the other hand 18 of 64 hypertensive diabetics (28 per cent.) and 11 per cent. of hypertensive controls gave a negative family history of hypertension, as opposed to 39 of 58 non-hypertensive diabetics (67 per cent.) and 72 per cent. of non-hypertensive controls. A statistical appreciation of these results is probably best achieved by omitting Group III, which provides little evidence for or against familial hypertension, and by comparing Group I with Groups II and IV taken together, thus distinguishing cases in which the familial incidence is definite from those in which it is doubtful or absent. It was thought worth while to keep the results for men and women separate. The two control series used are rather small, and show no significant differences from the corresponding diabetic figures. The only comparison which is significant is the one between hypertensive and non-hypertensive diabetics. The relevant data are as follows:

	Men: Groups		*Women: Groups*	
	I	II+IV	I	II+IV
Hypertensive diabetics	12	8	34	25
Non-hypertensive diabetics	9	25	10	21

The significance of the association between hypertension in the diabetic patient and evidence of familial hypertension is best measured by the use of the χ^2 test. For men we obtain $\chi^2 = 4{\cdot}63$, and for women $\chi^2 = 4{\cdot}27$. Both these values are significant; taking them together we have the joint value, with two degrees of freedom, $\chi^2_{(2)} = 8{\cdot}90$, for which the associated probability level is less than 2 per cent. Thus the significance of the association seems beyond reasonable doubt.

With regard to the factor of heredity in diabetes, 73 of the 209 diabetic patients (35 per cent.) gave a clear family history of the disease—46 of the 125 who were hypertensive (37 per cent.), and 27 of the 84 who were not hypertensive (32 per cent.). By comparison, four of the 50 hypertensive and three of the 50 non-hypertensive controls had family histories of diabetes. In making these inquiries we found that many of the patients also had a clear family history of obesity in parents or near relatives. In view of the well-known association of obesity both with hypertension and with diabetes, the figures representing these findings are also given. Although it is realized that such evidence obtained from individual patients is liable to error, it is reasonable to suppose that the total result would give a rough indication of the relative incidence of a family history of obesity in hypertensive and non-hypertensive diabetics. The results were as follows. Eight of 31 male hypertensive diabetics gave a family history of obesity, compared with nine of 46 non-hypertensive diabetics. Thirty-three of 94 female hypertensive diabetics gave a family history of obesity, compared

with six of 38 non-hypertensive diabetics. There is no apparent difference in this respect between hypertensive and non-hypertensive male diabetics. With female diabetics, on the other hand, the familial incidence of obesity is significantly greater (at the 5 per cent. level) in hypertensives (35 per cent.) than in non-hypertensives (16 per cent.).

Discussion

The inference drawn from these results is that heredity is a significant aetiological factor in the hypertension of diabetics over 40 years of age, and that such diabetic hypertension resembles the essential form in other ways. Further, the heredity of hypertension is evidently not linked with that of diabetes, for a positive family history of diabetes was obtained equally often in diabetics who were hypertensive and in those who were not. If, as it appears, the two hereditary factors—one, dominant, for hypertension, and one, probably recessive (Joslin, 1946), for diabetes—are independent, the Mendelian law of segregation of factors would be satisfied. The hypertension of diabetes resembles the essential form in several ways. In the first place, after the age of 40 years its incidence increases with age in the present diabetic series in the same way as it increases in the non-diabetic population. The control series of the present study is not a random sample from this point of view, and in Fig. 1 the statistics of Wetherby (1932), collected from a large unselected sample of the out-patient population, are used. Secondly, essential hypertension, like that of our diabetic patients, is considerably more common in women than in men. Thirdly, essential hypertension is frequently associated with obesity, and with the thick-set pyknic type of body build (Dunham, 1925; Hartman and Ghrist, 1929; Palmer, 1931; Robinson and Brucer, 1940), which are also features of a high proportion of the hypertensive diabetics in the present series. Fourthly, lability of blood-pressure was common in these patients, and is a characteristic of essential hypertension. Fig. 1 also shows that, as previous authors have reported, the incidence of hypertension above 30 years of age in the present series, and especially in women, was higher in diabetics than in non-diabetics. This difference might be due to the diabetes itself directly causing hypertension, or to some secondary effect resulting from the diabetes. If diabetes itself, or some factor associated with it, were a cause of hypertension, it would be reasonable to suppose that the longer a patient had had diabetes the more likely he would be to have hypertension. In Table IV and Fig. 4 this is shown to be the case with diabetics who have had the disease for more than five years. In those who have had diabetes for less than five years the incidence of hypertension is higher than would be expected, and some other explanation must be found. It has, however, to be remembered that the onset of diabetes in older patients is often symptomless, and is therefore difficult to date. It is true that all these diabetic patients were attending the diabetic clinic regularly, and it might therefore be argued that the harmful effects of their diabetes were neutralized by treatment. A word must therefore be said about the extent to which their diabetes was controlled. In this clinic the first consideration in treatment by

diet and insulin was to maintain a feeling of fitness and the ability to lead a normal life. Prevention of ketosis and adjustment of weight to the optimum were also aimed at. Complete control of glycosuria and a normal blood-sugar

TABLE IV

Incidence of Hypertension in relation to the Duration of Diabetes

Duration of diabetes	*Number*			*Hypertensive* %	*Average age (years)*		
	Total	*Men*	*Women*		*Total*	*Men*	*Women*
Under 6 months . .	18	8	10	72	61	64	56
6 months to 5 years .	64	25	39	64	60	58	61
All under 5 years . .	82	33	49	66	60	59	60
5–10 years . . .	43	13	30	46	57	50	59
10–15 ,, . . .	45	13	32	58	59	55	61
15–20 ,, . . .	19	9	10	63	60	59	62
20–25 ,, . . .	9	5	4	78	56	48	65

Total 198. In 11 patients the duration of diabetes could not be estimated.

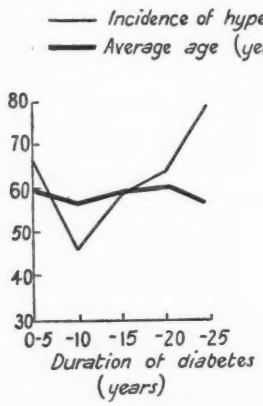

FIG. 4. Incidence of hypertension in relation to the duration of diabetes.

were not regarded as essential. Many elderly diabetics usually had a resting blood-sugar between 200 and 250 mg. per 100 ml. and sometimes more, and great care was taken to avoid hypoglycaemic reactions or any sudden lowering of the blood-sugar level. It will be clear therefore that metabolic control of the diabetic state was not complete enough to neutralize long-term effects, nor was there any certain indication that the degree of control was quantitatively related to the liability to develop cardiovascular degeneration. It would be expected therefore that any effect which diabetes itself has in raising blood-pressure would be apparent in Table IV and Fig. 4, and the figures show such an effect in those patients who have had diabetes for more than five years. There can be little doubt that diabetes itself is directly or indirectly a cause of cardiovascular degeneration and hypertension. This is shown by the observations that these disorders are more common among diabetics than among the general population in the same age-group, that their incidence increases with the duration of the diabetes irrespective of age, and that they are found con-

stantly in young diabetics at an age when such changes are almost unknown in other subjects. The fact that the incidence of such degenerations varies in different individuals, and that their degree and severity are not directly proportional to the severity of the diabetes, suggests that there may be other factors at work in producing them. The foregoing results indicate that among these other factors hereditary tendencies, such as an inborn liability to cardiovascular degeneration or obesity, may be important, and the figures presented give some idea of the extent to which hereditary tendencies operate. They also suggest that such genetic tendencies do not coincide with a diabetic heredity. Penrose (1950) said recently: 'The cause of every ailment known to medicine is influenced to a greater or lesser degree by the genetical structure of the individual patient. . . . We must however avoid imagining that genetical inquiry will lead us towards *the* cause of the condition except in the rarest cases.' No hard-and-fast conclusions can be drawn from the evidence submitted here. It does, however, suggest that a broad study of the genetical background of every patient with diabetes may be of value in assessing the ultimate prognosis.

In conclusion we should like to express our gratitude to Dr. Geoffrey Evans for kindly permitting one of us (H. W. B.) to study a control series of non-diabetic patients in his Out-patient Department at St. Bartholomew's Hospital, and to Mr. Norman T. J. Bailey, Statistician to the Department of Medicine in the University of Cambridge, for his assistance in assessing the significance of our figures.

Summary and Conclusions

The incidence of heredity as a causal factor in hypertension has been studied in a series of 209 diabetic patients and in a control series of 100 non-diabetic patients, of whom 50 had hypertension and 50 had a normal blood-pressure. All the patients were over 30 years of age. They were unselected except for the exclusion of patients with secondary hypertension and of those who were known to be mutually related. The conclusions are as follows:

1. When hypertension occurs in diabetics over the age of 40 years it resembles essential hypertension in its heredity, age incidence, and sex incidence. Diabetics over 30 years old show a considerably higher incidence of hypertension than that found in the general population. The incidence of a hypertensive family history is significantly greater among hypertensive diabetics than among diabetics with a normal blood-pressure. Omitting the group in which the evidence was indefinite, and taking men and women together, we find that 58 per cent. of hypertensive diabetics (46 out of 79) and 29 per cent. of non-hypertensive diabetics (19 out of 65) had a hypertensive family history.

2. In patients who have had diabetes for five years or more the incidence of hypertension increases with the duration of the diabetes, and this increase is unrelated to age.

3. A family history of diabetes occurs with about equal frequency in diabetics

who have hypertension (37 per cent.) and those who have normal blood-pressure (32 per cent.).

4. A family history of obesity was about twice as frequent in female hypertensive diabetics as among female non-hypertensive diabetics. This difference is significant. The corresponding figures in the case of male diabetics are not significant.

5. In assessing the remote prognosis of patients with diabetes, careful inquiry should therefore be made for indications of hypertensive disease or obesity in the family history.

The fact is emphasized that hypertension and atheroma, although often met with in the same patient, are not parallel conditions.

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THE USE OF RADIOACTIVE IODINE IN THE ASSESSMENT OF THYROID FUNCTION[1]

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Soon after radioactive isotopes of iodine became available they were applied to the investigation of thyroid physiology, and subsequently they have been widely used in the study and treatment of disease of the thyroid gland. The first investigations were made with I^{128} by Hertz, Roberts, and Evans (1938), but its short half-life of only 25 minutes limited its value. Hamilton and Soley (1939) used I^{131}, with a half-life of eight days, and this isotope has now become the standard agent used to study the pharmacological properties of iodine, the physiological role of the thyroid gland in human metabolism, and the behaviour of the gland when affected by disease. When radioactive iodine is administered orally or intravenously, a large part of the dose is collected by the thyroid gland, which can concentrate inorganic iodine to 10,000 times the level of iodine circulating in the blood (Hamilton, 1942). That part of the iodine which does not enter the thyroid gland is excreted by the kidneys at a rate which, in the absence of renal disease, is fairly constant, and which depends upon the concentration of circulating iodine. In some cases the radioactive iodine collected in the thyroid gland and excreted in the urine accounts for only 85 to 90 per cent. of the total dose administered; the remainder is mainly distributed throughout other body tissues, and some is excreted in the faeces, expired air, and sweat (Kelsey, Haines, and Keating, 1949). There is therefore a constant state of competition between the thyroid gland and the kidneys to collect circulating iodine, and any increase or decrease in thyroid activity is reflected in diminished or increased amounts excreted in the urine. In addition to studies of the normal and pathological physiology of the thyroid gland, much work has been carried out in an attempt to evolve with radioactive iodine a reliable test of thyroid function, and workers have approached the problem in different ways. The rate and extent of uptake of radioactive iodine by the thyroid gland has been fully investigated by several groups of workers since Hamilton and Soley (1940) made the early observations on patients with various types of goitre. Keating, Wang, Luellen, Williams, Power, and McConahey (1949) have assessed the value of such *in vivo* measurement of the quantity of radioactive iodine in the thyroid gland, and Werner, Quimby, and Schmidt (1949) have defined both the range of uptake in normal individuals and the deviations which occur in thyroid disease. Studies of

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the urinary excretion of the isotope have also been widely used as an indirect index of thyroid function. Keating, Power, Berkson, and Haines (1947) and Skanse (1949) made very careful analyses of the results obtainable by this method, and some workers in this country (Arnott, Emery, Fraser, and Hobson, 1949; Mason and Oliver, 1949) have felt that it provides a useful and accurate test for the diagnosis of thyrotoxicosis, especially if the urinary output during the 48 hours after administration of the isotope is subdivided into shorter periods. All workers agree, however, that the urinary excretion test alone does not differentiate clearly the normal from the abnormal in that important intermediate group of cases in which the diagnosis of thyrotoxicosis is clinically difficult and doubtful; and this is the group in which there is the most need for a reliable objective index of thyroid function. In an attempt to obtain more useful and accurate guidance to the state of thyroid function Keating, Wang, Luellen, Williams, Power, and McConahey (1949) developed the conception of a rate of iodide accumulation, as distinct from the absolute amount of iodide absorbed, by the thyroid gland. The same workers, and Myant, Pochin, and Goldie (1949), suggested the use of a thyroid clearance rate of plasma-iodide, analogous to the more familiar renal clearance rate of urea. The rate at which iodide is being absorbed by the thyroid gland is deduced from the curve of thyroid uptake obtained by external counting with a Geiger counter over the gland, the plasma concentration of radioactive iodine being determined simultaneously. Pochin (1950) has suggested that a simple clinical test, corresponding closely with the thyroid clearance of plasma-iodine, is provided by the ratio of the counts obtained, one hour after the dose, over the thyroid gland to the counts obtainable at the same time over the thigh. It is generally agreed that the presence of increased amounts of circulating thyroid hormone is responsible for the clinical manifestations of thyrotoxicosis, and any method of detecting such an increase should be a useful index of thyroid function. The work of Taurog and Chaikoff (1947) and of Leblond and Gross (1949) in animals has shown that circulating thyroid hormone is probably thyroxine itself. Taurog and Chaikoff (1947) used butyl alcohol extraction to separate the thyroxine, di-iodotyrosine, and inorganic iodine fractions of the total plasma activity due to circulating radioactive iodine, and came to the conclusion that about 90 per cent. of circulating iodine is in the form of thyroxine. Leblond and Süe (1941) showed that the di-iodotyrosine fraction of the protein-bound iodine is rapidly metabolized and broken down in plasma to form inorganic iodide. Our work has therefore been based on the assumption that an estimation of the protein-bound iodine, separated from the non-protein-bound fraction by precipitation with trichloracetic acid, is essentially a measure of the thyroxine content of the plasma. The estimation of protein-bound non-radioactive iodine is a standard method of assessing thyroid function, but it is an extremely difficult and laborious biochemical procedure, and unsuitable for routine application. The use of radioactive iodine enables thyroxine circulating in the blood to be easily 'labelled', so that it becomes readily detectable and measurable. Its estimation by this method should give valuable diagnostic help, and can be made relatively simply. This principle has

been applied by Freedberg, Ureles, and Hertz (1949), Clarke, Moe, and Adams (1949), and Williams, Jaffe, and Bernstein (1949).

The Present Investigation

Although a great deal of work has been done to clarify the physiological behaviour of the thyroid gland and of thyroxine, there is as yet little agreement as to the best way in which radioactive iodine may be used in the diagnosis of thyroid disease. Most observers have used a single test, and have compared the results obtained in normal and frankly thyrotoxic individuals. We decided to carry out in each patient all the investigations which promised to be of diagnostic help, and initially a series of normal and thyrotoxic subjects was fully investigated. We assessed the severity of the thyrotoxicosis by all the conventional clinical and laboratory methods available to us, assigning to each patient a figure (Grade 1 to Grade 4) to indicate the degree of abnormality. Having thus obtained a standard for normal and thyrotoxic subjects, we applied our results to a difficult intermediate group, the composition of which is discussed later. The present paper reports the results of this investigation, which was carried out in Sheffield and started in May 1948; the preliminary results have already been briefly reported (Miller and Wayne, 1949; Macgregor, 1950). The series comprises a total of 96 subjects, of whom 16 were completely normal as regards thyroid function, and had no evidence of any other endocrine disturbance. Forty-four patients were diagnosed as having primary thyrotoxicosis or toxic adenomata, the groups being composed of cases of all grades of toxicity from mild, border-line thyrotoxicosis (Grade 1) to thyrotoxicosis of the most severe degree (Grade 4). These gradings are essentially arbitrary in nature, and no high degree of accuracy is claimed for their figures; but they represent the final average opinion of at least three observers, each of whom took into account every clinical aspect of the case. Patients in Grade 1 showed least evidence of thyrotoxicosis, and some were only so classified after therapeutic trial with methyl thiouracil. The diagnosis was immediately obvious in patients in Grade 2, and the more severely affected patients were classified in Grades 3 and 4. Our 'intermediate group' consisted of 30 patients in whom no clinical evidence of toxicity was found after full and often prolonged study. Twenty-five patients in this group presented features of past or present thyroid disorder, such as non-toxic goitres, simple adenomata, and successfully treated or burnt-out thyrotoxicosis. There were also five patients who clinically presented symptoms which are often seen in thyrotoxicosis; but they had no thyroid enlargement, and an anxiety state was eventually diagnosed in each case. The patients included in this intermediate group are of the type which usually presents most difficulties with regard to diagnosis. In the Sheffield area, moreover, there is a high incidence of non-toxic goitre with slight enlargement of the thyroid gland, and this factor slightly increases the clinical difficulties when there are concurrent symptoms which may or may not be due to true thyrotoxicosis. We also studied four cases of myxoedema, one of Hashimoto's thyroiditis, and one of acromegaly. We investigated rather less fully, and have therefore not included,

about 20 cases of thyroid carcinoma. The results in no way conflict, as regards thyroid function as a whole, with the general statements we shall make.

Method of Investigation

All patients were admitted to hospital under the care of one of the authors (E. J. W.). The history was taken, and physical examination carried out, by three observers independently, and the final diagnosis and grading were discussed. All cases except the normal group were followed for long periods in the out-patient department, and in toxic cases the results of treatment were taken into account. We would emphasize the fact that the final decision as to whether an individual patient was thyrotoxic or not was only taken after the most thorough sifting of clinical evidence that we could devise. In no case were any of the observations using radioactive iodine taken into consideration in making the final classification. The collection of urine and blood specimens was also under our own supervision. This precaution is of great importance, since samples are readily lost or forgotten if close watch is not kept on house officers and nursing staff. Patients were fasting on the morning of the test, and the tracer dose of radioactive iodine was administered orally. The container was repeatedly washed out with water, and subsequently monitored to ensure that all the dose was taken. Patients were allowed to have lunch on the day of the test, usually about three hours after the tracer dose had been given, while observations of the uptake of the isotope by the thyroid gland were being made. All the specimens of urine passed were collected, and subsequently aliquot samples of 10 ml. of each specimen were examined for their content of radioactive iodine. At first we attempted to make estimations of blood activity with 0·5 ml. samples, but this method was found to be unsatisfactory because separate estimations of the protein-bound concentration could not be made with our technique. All the estimations of plasma concentration included in this paper were made with 20 ml. samples of blood withdrawn into a heparinized syringe. Samples of blood were usually taken one hour, three hours, and 48 hours after ingestion of the radioactive iodine.

Counting technique. The distribution of the radioactive iodine after ingestion was determined by normal Geiger counter technique. The amount of the active material taken up in the gland was assessed by means of a calibrated gamma-ray counter housed in a substantial lead shield. Lead diaphragms were introduced to produce a suitable collimation. The whole counter, with the associated pre-amplifier unit, was mounted on the arm of a modified mobile X-ray unit stand, so that it could be conveniently adjusted with respect to the patient. For calibration of the counter, measurements were made with a solution of radioactive iodine in a small glass phial, and by using glass models of the thyroid gland filled with an active solution. The counting rate produced by a concentrated source of active material placed in air at a known distance from the counter differs from the counting rate due to the same amount of activity in the gland at the same distance owing to scattering and absorption of the radiation in the tissues, and also because the activity is dispersed over a much greater

volume. In order to reduce the effect of absorption in the tissues a filter was introduced in front of the counter. This consisted of 1 mm. thickness of lead supported on a thin brass plate. The filter reduced to a negligible amount the effect of the soft component of the gamma-radiation of the radioactive iodine. It also had the effect of reducing to a small value the scattered radiation as measured by the counter. The difference between the count due to a point source in air and that due to the same source at the same distance, but backed by a block one cubic foot in size and consisting of unit density material, was only 3 per cent. By placing the point source at varying depths below the surface of the block it was found that the back-scatter into the counter compensated for the absorption in the superficial layers when the source was about 2·5 cm. below the surface. The effective radiation centre of the gland in the patient was obtained from a plot of the reciprocal of the square root of the counting rate against distance. In the majority of cases this effective radiation centre was approximately 2 cm. below the skin over the thyroid isthmus. Using the glass models of the thyroid gland filled with active material, and buried in unit-density scattering material in a model of the neck of a patient, we found that there was a close agreement between the counting rate due to the gland and that due to a concentrated source in air at the distance of the effective radiating centre. In preparing our build-up curves in the gland, we therefore deduced the calibration of the counter by measuring the concentrated source of radioactive iodine in its glass phial, and using this calibration after having deduced the effective radiating centre of the gland in question by the method described above. The effect of the filtration by 1 mm. of lead in reducing the magnitude of the scattered radiation may be seen by comparing the method adopted by Myant, Honour, and Pochin (1949). In their technique, using unfiltered radiation, the body tissues outside the immediate neighbourhood of the thyroid gland are screened from the counter, but a large correction of the order of 21 per cent. for scattered radiation is necessary. The filter used in our case causes a reduction in the counting rate to a value 0·6 times the unfiltered rate. In order to reduce errors due to variation in counter sensitivity, the overall sensitivity of the counting system was monitored by means of a source of radiocobalt placed in a standard position relative to the counter. The counter system was left switched on for the whole day when the build-up curve was being taken, and the scaler was protected from the influence of mains fluctuations by a manually operated Variac transformer. In plotting build-up curves it was our practice to count for a total of six minutes. This time was divided into two periods of two minutes with the counter axis at a distance of 27 cm. from the skin over the isthmus, while between these counts one count was taken with a block of lead supported above the isthmus. The lead was $1\frac{1}{2}$ inch (3·8 cm.) thick, and effectively cut out the radiation from the underlying gland, leaving a background which fell slowly with time as the active material in the rest of the body was distributed and eliminated. The lead block was large enough in area to eliminate radiation from the gland itself, but it also cut out some radiation from the normal tissues of the neck. Since at peak uptake the blood concentration was generally less than 1 per cent. per litre of plasma, the

amount of activity in the normal tissues of the neck underlying the lead block was certainly less than 0·5 per cent. of the ingested dose, and was considered negligible. This estimate was confirmed by the small counting rate observed over the thigh at a place where the cross-section was roughly the same as that of the neck. The actual counting rate for a dose of 20 μc. and for a 50 per cent. uptake under our conditions was approximately 350 counts per minute. The coefficient of variation (the standard deviation expressed as a percentage of the mean) for a particular point on the curve was generally less than 3 per cent. It is believed that our figures of peak uptake are correct to within 5 per cent., which is adequate for our purposes.

Liquid samples were counted in the liquid counter devised by Veall (1948). A thousandfold dilution of the stock solution was used as a standard. All liquids placed in the counter had a few milligrams per litre of sodium iodide introduced as carrier. Urine concentrations over the first 24 hours were high enough to make the statistical error small in counts of five minutes, and the error in estimating the total urinary output of radioactive iodine was influenced mainly by the adequacy of urine collection. If no sample was lost, the estimates of urine output were expected to be correct to within 5 per cent. No figures are quoted for tests in which a sample of urine containing an appreciable activity was lost. Blood samples were taken into heparinized bottles and centrifuged, and the plasma was then introduced into the counter. A blood plasma concentration of 1 per cent. per litre, with the usual tracer drink of 25 μc., gave about 25 counts per minute. Counts of at least 10 minutes were made on plasma samples. The background count was about 12 counts per minute. The statistical error in these results is much greater than in the other measurements, but it is estimated that the coefficient of variation of the individual blood measurements is less than 10 per cent. except for concentrations less than 0·3 per cent. of the ingested dose per litre. The estimation of the protein-bound iodine in the plasma was carried out by the technique used by Chaikoff, Taurog, and Reinhardt (1947), as follows. Ten ml. of the plasma were precipitated with 30 ml. of 10 per cent. trichloracetic acid. The suspension was centrifuged and the supernatant liquid poured off. The precipitate was then shaken with a further 30 ml. of trichloracetic acid, and the whole centrifuged again. After a repetition of this last procedure the precipitate was dissolved in 2N NaOH, and its activity was estimated. It was generally possible to dissolve the precipitated proteins from 8 ml. of plasma in 10 ml. of NaOH. Counts on protein-bound specimens were normally carried out for at least 15 minutes, and were subject to somewhat greater errors than those made on plasma specimens. With our present techniques of chemical preparation and of liquid counting, a tracer drink of 25 microcuries enabled us to obtain protein-bound specimens at 48 hours containing 0·4 per cent. of the ingested activity per litre, with a counting rate of eight counts per minute compared to a background rate of about 12 counts per minute. Any great reduction in ingested activity would lead to increased difficulties in measuring this organically bound fraction with sufficient accuracy for diagnostic value.

It is recognized that in using such amounts of radioactive iodine the dose of ionizing radiation given to the thyroid gland itself is not negligible, though the dose given to the rest of the body may be considered so; outside the thyroid this dose is everywhere less than 0·3 roentgen. If the uptake in the gland is 50 per cent., and the rate of biological elimination has a half-life of eight days, the dose given to a gland of normal size is approximately 35 r after a tracer drink of 25 μc. In the present series the doses given to the glands of the patients varied widely over a range of roughly 10 r to 100 r. The International Recommendations recently issued by the International Commission on Radiological Protection (1951) state that the maximum permissible dose received by radiation workers exposed to external radiation should be 0·3 r per week, even when the irradiation is confined to a particular organ or tissue. It is not known how far doses within the tolerance region can be considered cumulative, and whether it is legitimate, for example, to consider a dose of 15 r in any one year on a limited volume of tissue as equivalent in radiation danger to 0·3 r per week for 50 weeks. The International Commission on Radiological Protection does not make firm recommendations regarding the maximum permissible exposure to internal radiation. If we use the figure given for occupational exposure, a maximum permissible amount of radioactive iodine in the body is 0·3 μc., since this would give a dose rate in the gland of 0·3 r per week. It is clear that for patients undergoing diagnostic tests in which there is occasional exposure to radiation it is necessary to keep the dose down to the minimum possible level. Experimental work is in hand designed to give an increased sensitivity to measurements of the activity of the protein-bound iodine. In the meantime we have felt that tests on normal people should be made only once, and the 'normal' group is as small as could reasonably be expected to give representative figures. We have felt justified in using 30 μc. in cases in which there are reasonable grounds for suspecting thyroid disorder, though the tests have rarely been repeated on any patient in less than one year except where radioactive iodine therapy is intended. The practice of other workers has varied considerably as to the dose considered reasonable for diagnostic tests of this type. Some recently published work has suggested that tracer drinks should not normally be greater than 10 μc. (Arnott, Emery, Fraser, and Hobson, 1949; Tait, Cook, and Worsnop, 1951). This would give a dose of about 15 r which, averaged over one year, is about the recognized maximum permissible dose for occupational exposure. It has frequently been pointed out that radiation doses of the same order as those given in our tests are given as a routine to limited regions of the body in many X-ray diagnostic techniques. This is especially true of the skin in normal screening procedures (Martin, 1947; Braestrup, 1942). The effects of occasional exposures of this magnitude in such normal diagnostic work have not so far been considered to be serious.

Results

The data derived from the study of our patients are presented in Tables I, II, and III, with full particulars of the results of each test relating to every case.

TABLE I (*a*)

Results of Tests in Euthyroid Subjects

Case number	Sex	Age (years)	Diagnosis	Basal metabolic rate (%)	Blood-cholesterol (mg./100 ml.)	Gland uptake (%)		Time to ½ peak gland uptake (mins.)	Biological ½ life (days)	24-hrs. urinary excretion (%)	Thyroid clearances (ml./min.)				Plasma activity at 48 hrs. (% dose/litre plasma)			Remarks
						Peak	24 hrs.				1 hr.	2 hrs.	3 hrs.	½ peak	Total (*a*)	Protein-bound (*b*)	(*b*)/(*a*)	
1	F	50	Sarcoidosis	..	..	54	53	280	..	20·5	..	21	..	22	..	..	..	
2	M	48	A.F.	−16	..	31	29	308	..	44·5	18	12	..	18	neg.	neg.	..	Treated with digitalis
3	F	44	M.S.	..	..	26	26	360	2·3	59·5	..	5	..	10	0·19	..	..	Also rheumatoid arthritis
4	M	37	A.F.	..	..	35	32	260	..	48·0	21	19	16	16	0·1	neg.	..	Treated with digitalis
5	M	33	M.S.	..	..	21·5	19	480	..	51·8	11	..	4	..	0·12	neg.	..	Treated for congestive failure
6	M	60	Ophthalmoplegia	..	..	34·0	34·0	210	32	44·0	26	23	..	14	0·14	neg.	..	Died. Inconclusive autopsy
7	F	64	Parkinson's disease	+4	240	24·0	24·0	126	15·8	..	20	13	..	13	0·64	neg.	..	Also essential hypertension
8	F	25	M.S.	..	..	45·0	40·0	300	..	50	30	..	..	..	..	..	..	
9	F	64	P.A.	..	..	51·0	53·0	268	..	43	42·5	..	35·3	..	0·20	neg.	..	
10	M	45	..	..	..	47·0	42·0	260	..	33	38	25	..	30	..	..	..	
11	M	34	Dermatitis herpetiformis	..	210	37·5	34·0	250	..	55·7	45·8	..	16·7	..	neg.	neg.	..	
12	M	57	Peripheral arterio-sclerotic disease	0	210	34·0	31·0	390	..	53·0	24·0	15·0	..	14·0	0·07	neg.	..	Early dementia
13	F	37	M.S.	..	..	..	..	280	..	59·5	..	..	..	..	..	..	..	Gland readings omitted (counts inaccurately collimated)
14	F	30	Obesity	−11	255	53	53	260	4·6	37·0	30	37	34	46	neg.	neg.	..	
15	F	44	Obesity	−1	250	35	34	282	15·4	52·3	14·8	..	..	22·9	neg.	neg.	..	
16	M	60	Ophthalmoplegia	+13	300	49	46	380	17·7	40·2	30·5	..	10	..	neg.	neg.	..	

A.F. = auricular fibrillation (degenerative). M.S. = mitral stenosis. P.A. = pernicious anaemia. neg. = negligible.

The results are summarized in Table IV. It was not possible to carry out all investigations satisfactorily in every case, and when technical faults or inaccuracies in the collection or assessment of samples of blood or urine have made results unreliable, the figures have been omitted. The distribution of results of the investigations in all the patients tested is also presented in the form of histograms showing the following data: basal metabolic rate estimations (Fig. 1); the thyroid gland uptake of radioactive iodine at the peak point of its collection

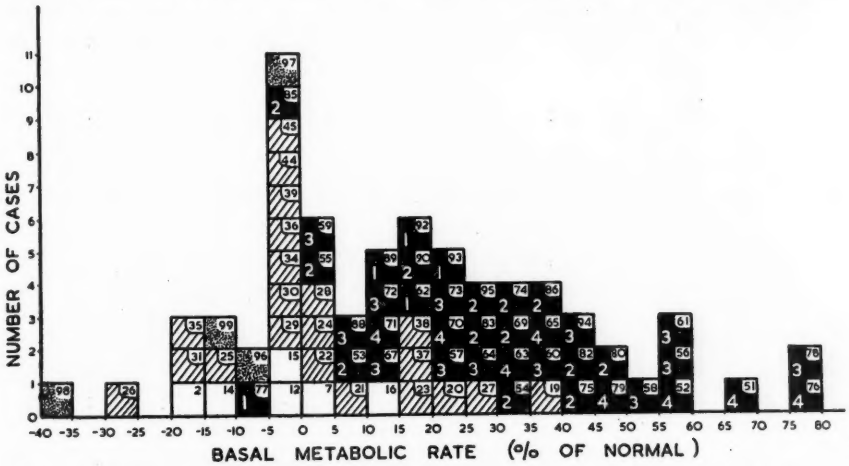

FIG. 1. Distribution of results of the basal metabolic rate estimations. In this and the following histograms clear white symbols indicate normal subjects, cross-hatched symbols patients in the intermediate group (see text), black symbols patients in the thyrotoxic groups, and stippled symbols patients with myxoedema. White figures on the black symbols indicate the grade of toxicity (see text); small black figures in the corner of each symbol refer to the Case numbers in Tables I–III.

of iodine (Fig. 2) and 24 hours after the dose was administered (Fig. 3); the distribution of the times which elapsed until half the peak uptake was reached (Fig. 4); the excretion of the isotope in the urine collected during the first 24 hours (Fig. 5); the thyroid clearance rates two hours after the dose was given, or at the time when the half-peak thyroid uptake was reached, whichever value was the higher (Fig. 6); the total plasma activity 48 hours after the dose (Fig. 8); and the plasma activity due to the protein-bound fraction of the same sample of plasma (Fig. 9). In order to assist recognition of individual cases, so that reference can be made to the Tables and to other Figures, the symbol representing each case bears the case number of that patient. The symbols of thyrotoxic patients also carry a figure representing the clinical grade of toxicity.

Basal metabolic rate. The estimation (Fig. 1) was carried out by the Douglas bag method, and the figures quoted are the mean of two or more consistent results. The test was not applied to all patients included in the normal group (Table I *a*), since we know that with our technique normal individuals may give readings lying between +20 and −20 per cent. On this basis 13 thyrotoxic patients out of 39 on whom the test was performed, or 33 per cent. of the total,

TABLE I (*b*)

Results of Tests in Intermediate Group

Case number	Sex	Age (years)	Diagnosis	Basal metabolic rate (%)	Blood-cholesterol (mg./100 ml.)	Gland uptake (%)		Time to ½ peak gland uptake (mins.)	Biological ½ life (days)	24-hrs. urinary excretion (%)	Thyroid clearances (ml./min.)				Plasma activity at 48 hrs. (% dose/litre plasma)			Remarks
						Peak	24 hrs.				1 hr.	2 hrs.	3 hrs.	½ peak	Total (*a*)	Protein-bound (*b*)	(*b*)/(*a*)	
17	F	45	T.T.	..	300	60	58	258	..	30·5	36	35	..	30	..	..	..	Thyroidectomy 1947. Auricular fibrillation
18	F	48	T.T.	..	290	43	41	180	..	50·0	18	15	20	20	..	..	..	Thyroidectomy 1942
19	F	45	N.T.G.	+36	210	46	46	132	22	31·8	43·7	..	27·6	..	0·29	0·15	51	Large gland. Basal metabolic rate unreliable. Dysphagia. Treated by operation
20	F	41	N.T.G. A.S.	+24	..	69	68	110	∞	32·8	33·0	..	..	45·0	0·13	neg.	..	
21	F	37	N.T.G. A.S.	+10	210	24	23·5	260	5	61·0	..	..	..	10·0	neg.	neg.	..	Had received iodine 2 months before
22	F	32	N.T.G.	+2	230	58	58·0	216	..	27·0	26·0	..	..	29·0	..	..	..	Small gland
23	F	39	N.T.G.	+18	200	42·5	42·0	130	14	40·5	..	..	55	38	0·32	..	..	Large gland. Treated by operation
24	M	20	N.T.G. A.S.	+3	200	48	45·5	220	5·1	40·5	20	27	28	56	neg.	neg.	..	Small gland. Treated by psychiatrist
25	F	61	N.T.G. A.S.	−11	210	42	40	316	..	35·0	20	20	18	13	0·18	neg.	..	Also essential hypertension
26	F	63	T.T.	−27	320	47	47	410	23·5	53·5	36	18	..	16	0·4	0·4	100	Also essential hypertension
27	F	39	T.T.	+27	375	41·5	41·5	170	24	48·5	34	22	..	30	neg.	neg.	..	Also mild anxiety state
28	F	58	A.S.	+2	240	33·0	33·0	238	116	50·8	13·6	..	..	23·5	1·16	neg.	..	Large cervical lipoma overlying thyroid
29	F	47	A.S.	−5	210	48·0	48·0	162	15·4	37·0	..	..	25	25	0·3	..	..	Very neurotic
30	F	27	N.T.A.	0	200	52	50·0	153	∞	40·0	47·0	59·0	55·0	53·0	0·09	neg.	..	Treated by operation for simple adenoma
31	F	32	A.S.	−18	225	58·0	56·0	146	13·0	32·0	..	58	70·0	58·0	0·16	..	..	
32	F	47	T.T. A.S.	..	..	42	38	240	..	47·5	..	..	..	..	..	..	..	
33	F	31	N.T.A. A.S.	..	290	42	38	180	..	48·9	30·2	..	..	39·3	0·06	neg.	..	
34	F	18	N.T.G.	0	150	47	46·5	300	..	41·0	..	..	..	..	..	..	..	

35	F	33	N.T.G.	−18	270	43	43	280	40	41·0	..	..	45	..	..	..	..
36	F	28	N.T.G. A.S.	−3	320	58	57	186	12	33·1	58	..	71	71	neg.	neg.	..	Small goitre. Many symptoms of toxicity
37	F	20	N.T.G. A.S.	+20	190	64·5	64·5	146	70	24·0	62	64	..	69	0·18	neg.	..	Small goitre. Anxiety state
38	M	32	T.T.	+20	140	50·0	50·0	171	19·6	38·4	..	..	56·5	..	0·1	0·09	93	Invalided from R.A.F. 1942 with thyrotoxicosis
39	F	27	N.T.G.	−3	183	42·0	36·0	310	..	48·4	21·6	..	..	17·8	neg.	neg.	..	Thyrotoxicosis diagnosed 1942
40	F	37	A.S.	..	270	46·0	44·0	286	..	40·8	21·6	..	30·6	..	0·19	neg.	..	
41	F	55	N.T.G.	..	..	37·0	35·0	310	..	49·6	..	..	17·9	..	neg.	neg.	..	
42	F	37	A.S.	..	330	49·0	49·0	145	..	48·8	30·0	..	25·0	30·0	0·1	neg.	..	
43	F	42	N.T.A.	..	280	43·0	43·0	212	..	52·3	21·0	..	17·0	17·0	0·2	neg.	..	? Cold nodule
44	F	33	T.T. A.S.	−3	320	56·5	56·5	108	9·5	32·0	69·0	..	39	60·0	0·44	0·35	80	Thyroidectomy 1946
45	F	62	N.T.G.	−3	..	54·0	54·0	226	30·0	37·8	36	..	31	31·0	neg.	neg.	..	Cataract. Pernicious anaemia
46	F	46	T.T. A.S.	..	385	55·5	55·5	238	14·8	40·0	39·7	..	39·1	39·1	neg.	neg.	..	

A.S. = anxiety state. No goitre. N.T.A. = non-toxic adenomatous goitre. N.T.G. = non-toxic diffuse goitre. T.T. = thyrotoxicosis in remission, natural or due to past treatment. neg. = negligible.

TABLE II (*a*)

Results of Tests in Thyrotoxicosis

Case number	Sex	Age (years)	Grade of toxicity	Basal metabolic rate (%)	Blood-cholesterol (mg./100 ml.)	Gland uptake (%)		Time to ½ peak gland uptake (mins.)	Biological ½ life (days)	24-hrs. urinary excretion (%)	Thyroid clearances (ml./min.)				Plasma activity at 48 hrs. (% dose/litre plasma)			Remarks
						Peak	24 hrs.				1 hr.	2 hrs.	3 hrs.	½ peak	Total (*a*)	Protein-bound (*b*)	(*b*)/(*a*)	
51	F	34	4	+66	150	88	75·5	28	3·8	8	..	..	..	..	..	..	..	Treated with M.T.
52	F	57	4	+56	210	72·5	72·5	68	33·0	12·5	..	..	..	..	..	..	..	Treated with I^{131}
53	F	28	2	+10	185	70·5	70·5	106	13·0	22·5	96	100	..	..	0·42	0·41	98	Treated by operation
54	F	53	2	+33	230	65	58	90	3·9	11·9	..	184	..	..	2·0	1·35	68	Also carcinoma. Treated with M.T. and D.X.R.
55	F	55	2	+3	250	..	71	..	..	20·0	..	..	..	..	..	..	..	Limited observations. Treated with I^{131}
56	F	33	3	+60	200	88	82	24	8·0	5·6	458	..	298	..	0·68	0·52	76	Treated by operation
57	F	38	3	+24	..	79	77	90	23·0	24·3	..	..	..	..	..	..	..	Treated with M.T.
58	F	58	3	+53	190	77	65	30	6·0	5·0	450	..	..	..	..	..	..	Treated with M.T.
59	F	22	3	+2	275	77	77	125	13·0	16·0	..	245	250	232	1·04	1·06	100	Treatment with M.T. failed. Subsequent operation
60	F	39	3	+40	155	76	73·5	24	5·4	4·2	250	..	..	383	0·98	1·0	100	Large gland. Treated with I^{131}
61	M	34	3	+59	160	72	72	96	16·1	20·8	121	..	169	..	0·24	0·13	54	Treated with M.T.
62	F	38	1	+17	195	63	62·5	145	5·3	20·0	58	76·8	121	97	1·26	1·05	83	Not fasting. Treated with M.T.
63	F	24	4	+32	200	82·5	76·5	10	10·0	5·5	550	560	..	..	0·87	..	..	Treated by operation
64	F	20	3	+26	205	75·5	55	37	2·0	8·6	200	220	..	215	5·5	3·4	62	Operation and M.T. failed. Treated with I^{131}
65	F	42	4	+40	230	90	79	24	7·0	10·3	226	..	103	..	2·2	1·6	74	Treated with I^{131}
66	F	45	4	..	..	76·5	71	42	15	15·5	..	153	..	..	..	..	..	Congestive failure. Died later
67	F	31	3	+15	150	81·0	74	50	5·3	9·0	111	111	315	123	..	..	..	Also severe thrombocytopenic purpura. Treated with iodine
68	M	22	4	..	200	70·0	67·5	41	4·8	3·5	163	244	..	210	0·96	0·74	75	Large gland. Tracheal compression. Treated by operation
69	M	54	2	+34	220	61·0	56·0	100	12·8	21·3	92	..	99	82	1·03	0·87	84	Treated with I^{131}
70	F	46	4	+24	170	82·5	82·5	120	..	15·5	..	..	..	..	..	..	..	Treated with I^{131}
71	F	28	4	+14	220	92·0	72·0	27	4·6	10	184	280	..	320	2·9	..	..	Treated with M.T.
72	M	38	3	+12	75	77·0	74·0	80	7·0	10·5	145	174	..	159	1·6	0·91	57	Treated with I^{131}
73	M	49	3	+22	230	72·0	70·0	85	8·5	28·0	84	57	..	67	0·87	0·63	72	Treated with M.T.

74	F	47	2	+32	200	57·0	54·5	104	32·0	34·5	..	43	..	50	0·64	0·64	100	Previous operation. Treated with I^{131}
75	F	47	2	+43	130	61·0	61·0	102	4·7	28·5	..	30	29	28	1·5	1·2	79	Previous operation and D.X.R. Treated with I^{131}
76	F	60	4	+80	195	75·0	64·0	39	5·0	8·5	270	..	..	210	3·5	2·9	84	Malignant exophthalmos. Treated with I^{131}
77	F	45	1	−7	190	70·0	70·0	117	..	23	75	76	..	79	..	..	..	Treated with M.T.
78	F	33	3	+80	175	89·0	72·5	36	2·8	7	..	..	..	250	..	..	..	Treated with M.T.
79	F	36	4	+46	230	92·0	72·0	67	3·9	8·8	612	..	171	612	2·3	1·6	70	Admitted with failure. Treated with M.T. and I^{131}
80	F	21	2	+49	195	88·0	87·0	90	7·2	3·3	..	..	347	578	0·78	0·61	77	Treated with M.T. and operation
81	F	34	3	..	200	89·0	87·0	35	..	4·7	885	..	250	..	1·29	0·86	67	Treated by operation
82	M	51	2	+42	220	86·0	78·0	44	8·5	3·6	833	..	187	800	1·48	1·43	97	Treated with I^{131}
83	F	47	2	+29	112	88·0	76·0	48	8·8	6·0	1780	..	..	1,780	1·77	1·24	76	Treated with I^{131}

A.F. = auricular fibrillation. D.X.R. = deep X-ray therapy. I^{131} = radioactive iodine. M.T. = methyl thiouracil. Operation = partial thyroidectomy.

TABLE II (*b*)

Results of Tests in Toxic Adenoma

Case number	Sex	Age (years)	Grade of toxicity	Basal metabolic rate (%)	Blood-cholesterol (mg./100 ml.)	Gland uptake (%)		Time to ½ peak gland uptake (mins.)	Biological ½ life (days)	24-hrs. urinary excretion (%)	Thyroid clearances (ml./min.)				Plasma activity at 48 hrs. (% dose/litre plasma)			Remarks
						Peak	24 hrs.				1 hr.	2 hrs.	3 hrs.	½ peak	Total (*a*)	Protein-bound (*b*)	(*b*)/(*a*)	
85	F	55	2	0	195	56	55	140	..	31·5	..	..	..	..	..	..	..	A.F. Treated by operation and digitalis
86	F	33	2	+36	200	63·5	63	134	25	31	62	..	..	70	0·25	..	..	Treated by operation. Large gland
87	F	52	1	..	270	60	60	136	12	21·0	60	82	..	84	0·74	neg.	..	n.a. = 3×s.g.a. Treated by operation
88	F	56	3	+7	380	76	76	20	15	3·5	..	..	..	..	..	..	..	Treated by operation. Large gland
89	F	42	1	+13	275	62	60	126	16	28	..	36	..	36	1·15	0·82	71	Treated by operation. n.a. = 2×s.g.a.
90	F	65	2	+18	200	71·5	63·5	108	6	7·5	..	36	..	..	..	..	..	Treated by operation
91	F	73	3	..	140	70·0	67·5	41	4·8	1·2	..	330	..	..	3·07	2·45	80	A.F. Congestive failure. Treated with I^{131}
92	F	53	1	+17	290	62·0	62·0	104	14·0	29·0	65	..	39	..	0·63	..	..	n.a. = 2×s.g.a. Treated with I^{131}
93	F	26	1	+23	140	65·0	64·5	135	..	34·0	..	..	..	..	..	..	..	Treated with M.T.
94	F	56	3	+43	165	62·0	57·0	36	4·7	6·0	..	..	..	..	2·4	1·1	47	Treated by operation
95	F	58	2	+30	165	60·5	60·5	77	70	12·0	100	87	..	89	2·12	1·5	71	A.F. Congestive failure. Treated with M.T.

A.F. = auricular fibrillation. I^{131} = radioactive iodine. M.T. = methyl thiouracil. Operation = partial thyroidectomy. neg. = negligible. n.a. = nodule activity. s.g.a. = surrounding gland activity.

TABLE III

Results in Other Conditions

Myxoedema

Case number	Sex	Age (years)	Basal metabolic rate (%)	Blood-cholesterol (mg./100 ml.)	Gland uptake (%)		Time to ½ peak gland uptake (mins.)	Biological ½ life (days)	24-hrs. urinary excretion (%)	48-hrs. urinary excretion (%)	Thyroid clearance (ml./min.)	Plasma activity at 48 hrs. (% dose/litre plasma)		Remarks
					Peak	24 hrs.						Total	Protein-bound	
96	F	61	−8	390	12·5	12·5	280	11·9	46	62	5	0·4	neg.	Also diabetes
97	F	59	0	315	4·0	3·5	..	..	..	..	..	..	..	
98	M	62	−42	645	8·0	6·3	..	..	43	45	0·4	0·7	neg.	
99	F	64	−52	420	23·4	22·5	260	7·0	56·5	63·3	34	..	..	Also Raynaud's disease

Hashimoto's thyroiditis

Case number	Sex	Age (years)	Basal metabolic rate (%)	Blood-cholesterol (mg./100 ml.)	Gland uptake (%)		Time to ½ peak gland uptake (mins.)	Biological ½ life (days)	24-hrs. urinary excretion (%)	Thyroid clearances (ml./min.)				Plasma activity at 48 hrs. (% dose/litre plasma)			Remarks
					Peak	24 hrs.				1 hr.	2 hrs.	3 hrs.	½ peak	Total (a)	Protein-bound (b)	(b)/(a)	
100	F	43	−20	300	45	37	47	1·7	36	59	36	..	68	2·7	2·3	87	Treated by D.X.R.
Acromegaly																	
101	M	43	+1	275	54	53	180	∞	29·4	61·8	..	97·7	97·7	neg.	..	..	Treated by D.X.R.

D.X.R. = deep X-ray therapy. neg. = negligible.

TABLE IV

Summary of Results in Tables I–III

Cases		*Basal metabolic rate (%)*	*Blood-cholesterol (mg./100 ml.)*	*Gland uptake (% dose)*		*Time to ½ peak uptake (mins.)*	*24-hrs. urinary excretion (% dose)*	*Thyroid iodide clearance rate (ml./min.)*	*48 hrs. plasma activity (% dose/litre)*	
				Peak	*24 hrs.*				*Total*	*Protein-bound fraction*
Normal (16)	Range	−16 to +13	210–300	21–54	19–53	126–480	20–59	10–46	0–0·64	0
	Mean	−2	244	38	37	293	46	24	0·12	0
Intermediate (30)	Range	−27 to +36	140–385	24–69	23–68	108–410	24–61	10–71	0–1·16	0–0·4
	Mean	+3·5	248	48	47	215	41	36	0·19	0·05
Normal + intermediate (46)	Mean	..	..	45	44	242	43	32	0·16	0·03
Thyrotoxicosis (33)	Range	−7 to +80	75–275	57–92	54–87	10–145	3–34	30–1,780	0·24–5·5	0·13–3·4
	Mean	+34	192	78	71	66	13	346	1·56	1·15
Toxic adenoma (11)	Range	0 to +43	140–380	56–76	55–76	20–140	1–34	36–330	0·25–3·07	0–2·45
	Mean	+21	220	64	63	96	19	100	1·48	1·17
Thyrotoxicosis + toxic adenoma (44)	Mean	..	..	74	69	74	14	297	1·53	1·15
Myxoedema (4)	Range	0 to −42	315–645	4–23	3–22	..	43–56	0·4–34	0·4–0·7	0
	Mean	−18	442	12	11	..	48	13	0·5	

had 'normal' basal metabolic rates, and included in that number are five with moderately severe or very severe degrees of toxicity (Cases 59, 67, 71, 72, and 88). In addition three patients with a non-toxic goitre or anxiety state had basal metabolic rates in excess of +20 per cent. These figures serve to confirm the generally accepted view that an estimation of the basal metabolic rate is of doubtful value in differentiating between thyrotoxicosis and other conditions when there is clinical doubt regarding the diagnosis. It is of interest that Keating, Haines, Power, and Williams (1950), in their study of the value of radioactive iodine as a diagnostic aid, found that, if the Mayo Foundation standard deviation of the basal metabolic rate at any age (6·9 per cent.) were accepted, 51 per cent. of their euthyroid patients had values outside the normal range of +13 to −13 per cent. ($\pm 2\sigma$). Bartels (1950) found the basal metabolic rate to be below +20 per cent. in 8 per cent. of a series of 1,000 thyrotoxic patients, and in some cases a normal basal metabolic rate was found in the presence of severe thyrotoxicosis, a finding which we have noted in the present series (Cases 59, 67, 71, 72, and 88). Furthermore, a raised rate occurs in many conditions other than thyrotoxicosis, such as heart failure and pyrexia, and an apparently raised rate is not uncommonly found in some anxiety states. We therefore agree with those who regard an estimation of the basal metabolism as of little help in doubtful cases, rather than with Simpson (1948), who stated that a normal basal metabolic rate is never found in thyrotoxicosis. We have recorded in the present study all the results of basal metabolic rate estimations, so that the value of this traditional investigation in cases of suspected thyrotoxicosis may be compared with the results of the more specific tests of thyroid function using radioactive iodine.

Thyroid gland uptake. The gland uptake of radioactive iodine at the peak value is shown in Tables I to III, and is charted in Fig. 2. In the normal group the uptake was in the range of 21 to 54 per cent. of the administered dose, with a mean of 38 per cent. The intermediate group had a somewhat similar range, with a mean of 48 per cent., with the important exception that there were eight patients who had a peak uptake of over 55 per cent. (Cases 17, 20, 22, 31, 36, 37, 44, and 46). These eight cases overlap with the toxic group of 44 patients, all of whom had peak uptakes of 56 per cent. or greater, the highest uptake in our series being 92 per cent. in two cases (Cases 71 and 79) and the mean of the group 74 per cent. All the toxic group had uptakes greater than any recorded in the normal group, and three of the four patients with myxoedema had the lowest uptakes recorded. The uptake by the gland at 24 hours (Fig. 3) shows the same pattern of distribution as the peak uptake, but even more overlap is apparent between the toxic and intermediate or normal categories. No less than 12 intermediate or normal cases appear in the same overlap area in the figure as 21 toxic cases, but the greatest overlap occurs in the 50 to 60 per cent. range. In many toxic cases there is a drop in the 24-hour value as compared with the peak uptake, and this fall in the amount of iodine retained in the gland is due to its conversion into thyroxine and transfer into the blood, a transfer known to correspond with a rise which occurs in the activity of plasma by that time. The

fall in gland activity may be very considerable, as in Case 64, where a peak uptake of 75·5 per cent. had diminished to 55 per cent. by 24 hours, and in Cases 71 and 79, where the drop was in each case from 92 to 72 per cent. The gland uptake after 24 hours does not give as true an indication of the avidity of the gland for iodine as does the peak uptake, but it enables use to compare our values with those published by Werner, Quimby, and Schmidt (1949) in one of the largest series so far reported. Our range of normal uptakes is 19–53 per cent.,

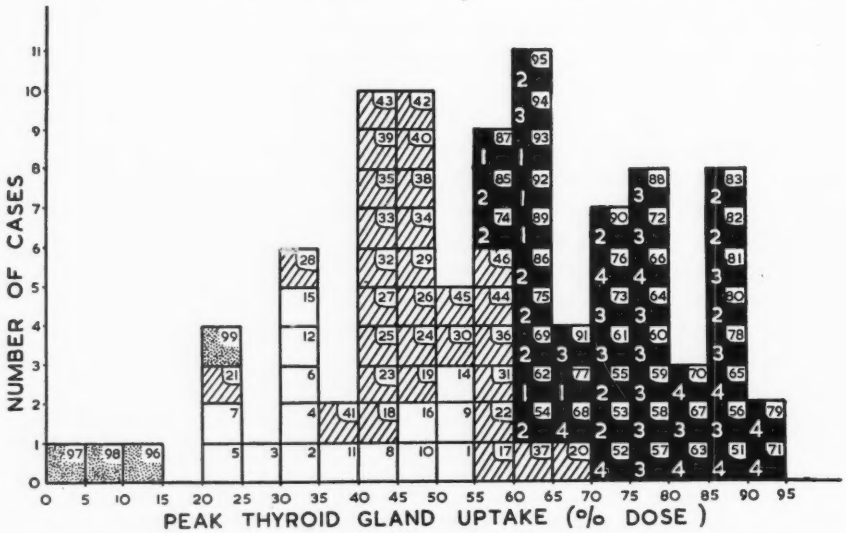

FIG. 2. Distribution of estimations of the peak thyroid gland uptake of radioactive iodine. (For explanation of symbols see Fig. 1.)

compared with a range of 7–49 per cent. in the American workers' series of 57 normal controls. But whereas only six (10 per cent.) of their patients had uptakes greater than 35 per cent., there are five patients (33 per cent.) in our normal group with uptakes of this order. We believe these differences to be significant, and to be possibly connected with the known lack of iodine in the Derbyshire area (Murray, Ryle, Simpson, and Wilson, 1948). It is recognized that thyroid glands with a low iodine content from any cause have an increased avidity for iodine, and Leblond and Mann (1942) showed that continued dietary deficiency of iodine led to increased collection of iodine by the thyroid gland. There is scarcely any overlap between the patients with thyrotoxicosis and the normal controls in respect of their peak and 24-hour uptakes, but there were eight patients in the intermediate group, with no evidence of toxicity, who had either anxiety states or non-toxic goitres, and who had uptakes of 56 per cent. or greater, and so overlapped with the toxic group. In the group studied by Werner, Quimby, and Schmidt (1949) no less than 40 out of 97 thyrotoxic patients had uptakes within the limits observed in their control subjects. If in their series 40 per cent. is taken as the upper limit of normal, only four per cent.

of their normal cases fall in the toxic range, but 11 per cent. of their toxic cases then lie in the normal range. Luellen, Keating, Williams, Berkson, Power, and McConahey (1949) noted that some euthyroid patients with nodular goitres may at times collect more radioactive iodine in the thyroid gland than other euthyroid subjects, and they concluded that adenomatous goitres, especially large ones, ought not to be regarded as entirely normal in function, even in the absence of clinical hyperthyroidism. Werner, Quimby, and Schmidt (1949) and Myant,

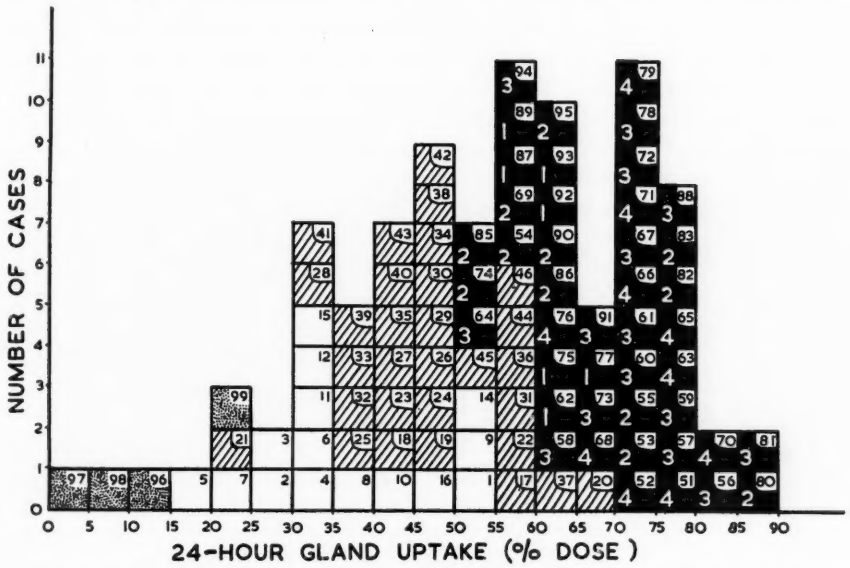

FIG. 3. Distribution of estimations of the thyroid gland uptake 24 hours after a dose of radioactive iodine. (For explanation of symbols, see Fig. 1.)

Pochin, and Goldie (1949) also mentioned cases of non-toxic goitre with uptakes of this order; the former workers noted, in a series of patients investigated when in remission of hyperthyroidism as a result of various types of treatment, that the iodine uptake often continued at an elevated level, despite the regression of symptoms and the return of the basal metabolic rate to normal. We feel that findings such as these, as well as similar observations made by us after effective therapeutic doses of radioactive iodine (Blomfield, Jones, Macgregor, Miller, and Wayne, 1951), show that unusually high uptakes of radioactive iodine by the thyroid gland may exist without overactivity of the gland as judged by other criteria.

The peak and 24-hour uptake in patients with toxic adenomata was, in general, lower than that of the group with diffuse thyrotoxicosis, the mean peak uptake in the adenomatous group being 64 per cent. as compared with 78 per cent. in the remaining toxic cases. Our equipment was not sufficiently collimated to enable us to decide whether the activity in the adenomata was significantly higher than that in the surrounding thyroid tissue; such findings were discussed

by Means (1949) with regard to the function of isolated thyroid adenomata. In five cases, however (Cases 86, 87, 89, 92, and 95), it appeared that the greatest amount of activity present in the gland was concentrated in the palpable adenoma. Two patients in the toxic group, Cases 74 and 75, with two of the lowest uptakes, 57 and 61 per cent. respectively, had previously had thyroidectomy, and the lesser amount of active thyroid tissue may be related to the smaller uptake of radioactive iodine which was found in spite of their undoubted toxicity. It therefore appears that when the volume, or mass, of hyperfunctioning thyroid tissue is small, for example in nodular recurrences after partial thyroidectomy or in the case of toxicity due to the presence of an adenoma, the absolute amount absorbed by the gland as a whole is of less diagnostic value than when the thyrotoxicosis is due to diffuse enlargement of the gland, as in typical Graves' disease. This conclusion agrees with the observation of Keating, Haines, Power, and Williams (1950) that, no matter by what technique the concentration of radioactive iodine in the thyroid gland is measured, there is a significant overlap with the euthyroid range, and that tracer tests for radioactive iodine, as carried out by them, were of limited value in indicating the presence or absence of hyperthyroidism in cases of adenomatous goitre. A further point of interest that emerged from the present investigation was that a relationship appeared to exist between the severity of the thyrotoxicosis, as assessed independently on clinical grounds, and the uptake of iodine by the gland. In the histograms of peak uptake (Fig. 2) and 24-hour uptake (Fig. 3) it can be seen that there is a tendency for cases of Grade 3 and Grade 4 toxicity to fall among the upper values, and for those of Grades 1 and 2 to fall among the lower values, of the toxic group. If the 'mean grade' of severity is estimated for each column of toxic cases in Fig. 2, there is a gradual rise of severity from a 'mean grade' of 1·6 in the group with a peak uptake of 56 to 60 per cent., through successive 'mean grades' of 1·7, 2·6, 2·8, 3·1, 3·6, and 2·9, to a 'mean grade' of 4 in the 91 to 95 per cent. column. A similar rough correlation exists in the figures representing the 24-hour uptake.

Time to half-peak uptake. The rate of uptake of radioactive iodine by the thyroid gland is a measure of thyroid function which has been assessed in various ways by different groups of workers. A very simple measure of the rate at which the iodine is being removed from the blood by the thyroid is the time which elapses until half the maximum gland uptake has been achieved (the time to the half-peak value). Observation of this value by serial *in vivo* measurements of gland activity after administration of a tracer dose shows clearly that thyrotoxicosis is characterized by a very much shorter time to half-peak than that which occurs in normal individuals. The values in the present investigation are shown in Fig. 4. In this series all thyrotoxic patients had times which were over an hour shorter than 14 of the 15 normal controls. The time to half-peak is a measure of the slope of the curve of uptake of radioactive iodine into the gland, and is affected by the rate of absorption of the oral dose of radioactive iodine, a variable which has induced some workers to use the intravenous route for administering tracer doses (Pochin, 1950). The longest time in our toxic

group was found in a patient (Case 62) who through a misunderstanding received a light breakfast some two hours previously. Some of the other more prolonged times are undoubtedly related to variable rates of absorption from the bowel, quite apart from the rate at which the thyroid gland absorbed circulating iodide. The mean time to half-peak of the whole toxic group was 74 minutes, that of the intermediate group 215, and of the normals 293 minutes. Myant, Pochin, and Goldie (1949) quoted values of 280 minutes for their control

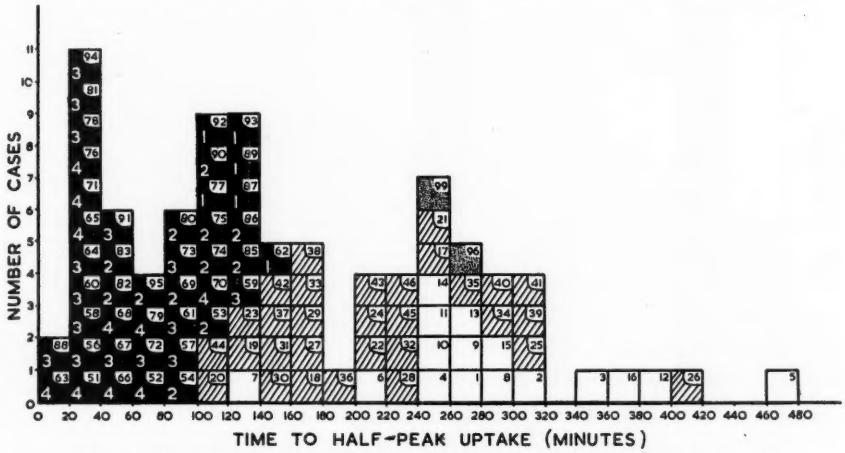

FIG. 4. Distribution of estimations of the time to half-peak gland uptake. (For explanation of symbols, see Fig. 1.)

group and 54 minutes for their toxic group. There is, however, a significant overlap between the groups in the present series, and a half-peak time between 100 and 150 minutes can occur in a normal, an intermediate, or a toxic case. It will be noted that many cases in the intermediate group which occupy positions in the overlap zone are in similar positions in the histograms showing gland uptake. The slow rise of gland uptake, and uncertainty regarding the time when maximum absorption is attained, make it difficult to assess the time to half-peak in myxoedema, but it is probably within the normal range.

Twenty-four-hour urinary excretion. The values for the 24-hour urinary excretion of radioactive iodine show a distribution which is the reverse of that of gland uptake, toxic patients excreting the smallest amounts (Fig. 5). There is a very considerable overlap when the figures for bulked 24-hour urine excretion are used. No less than 11 normal or non-toxic patients had urinary excretions within the same range as 14 patients with thyrotoxicosis, the overlap arising in the range from 20 per cent. to 35 per cent. of the administered dose. Marinelli, Quimby, and Hine (1948) found the test more useful if the excretion during the first six hours was neglected, and Mason and Oliver (1949) and Arnott, Emery, Fraser, and Hobson (1949) further subdivided the 48-hour period. We have restricted our observations to 24-hour samples, and agree with the latter workers that it is not a practical procedure to apply the mathematical analysis

of Keating, Power, Berkson, and Haines (1947) as a routine in all cases owing to the obvious unreliability of urine collection, especially in female patients, and owing to the intrinsic inaccuracies of the method. Skanse (1949) pointed out that the extent of overlap between thyrotoxic and euthyroid patients has varied considerably in different studies, and probably depends to a great extent

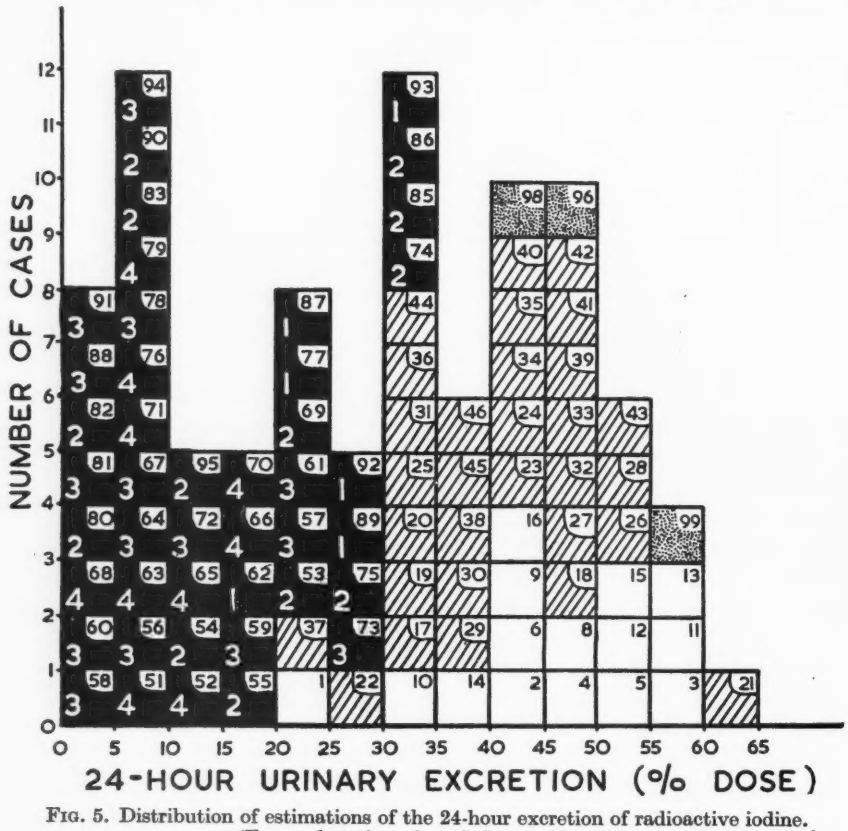

FIG. 5. Distribution of estimations of the 24-hour excretion of radioactive iodine. (For explanation of symbols, see Fig. 1.)

upon the type of case studied. As in the case of thyroid gland uptake, some patients with non-toxic goitres may have urinary excretions of radioactive iodine which are intermediate between those found in normal controls and those which are typical of thyrotoxicosis, and in some cases, such as those described by Fraser (1949), the test may actually suggest frank thyrotoxicosis. Fraser pointed out that there is a trend towards a less abnormal urinary excretion as the diagnosis of thyrotoxicosis becomes less certain, and this trend is evident in Fig. 5. We agree with McArthur, Rawson, Fluharty, and Means (1948), who stated that a low urinary excretion of the isotope is a useful and valuable indication of thyrotoxicosis, but that intermediate degrees of excretion are of no diagnostic help. A high urinary excretion definitely excludes thyrotoxicosis in

patients with a raised basal metabolic rate due to such conditions as anxiety states, hypertensive heart disease, Parkinsonism, phaeochromocytoma, alcoholism, or the ingestion of excessive quantities of thyroid extract.

Thyroid clearance rate. Another index of the rapidity of uptake of iodide by the thyroid gland is the plasma-iodide clearance rate, a measure of the volume of plasma completely cleared of iodide by the thyroid in unit time. The clearance rates of the subjects in the present investigation are charted in Fig. 6, and

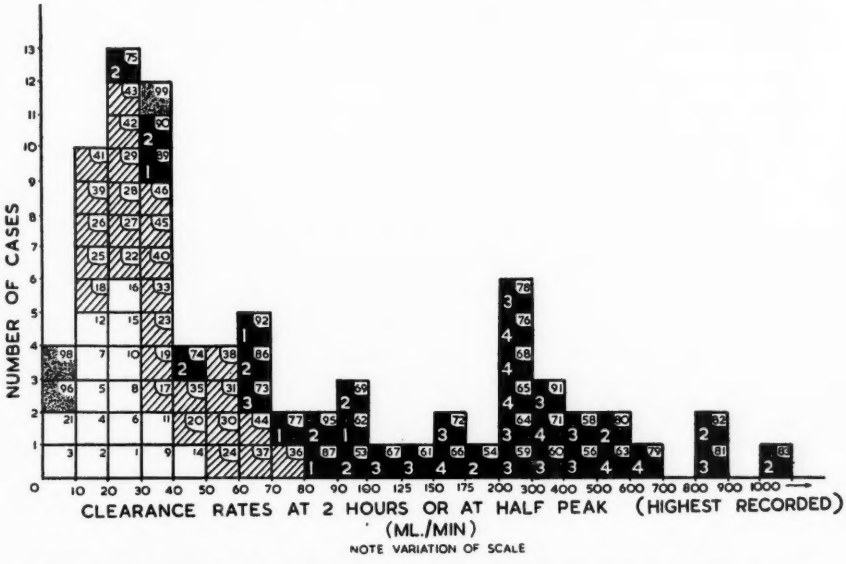
NUMBER OF CASES
0 10 20 30 40 50 60 70 80 90 100 125 150 175 200 300 400 500 600 700 800 900 1000
CLEARANCE RATES AT 2 HOURS OR AT HALF PEAK (HIGHEST RECORDED)
(ML./MIN)
NOTE VARIATION OF SCALE

FIG. 6. Distribution of estimations of the thyroid clearance rates of plasma-iodide. (For explanation of symbols, see Fig. 1.)

show mean clearances of 24, 36, and 297 ml. per minute in the normal, intermediate, and toxic groups respectively. There is not, however, the clear-cut separation between toxicity and normality described by Myant, Pochin, and Goldie (1949). Our highest normal clearance rate was 46 ml. per minute, but we found higher clearance rates in seven subjects in the intermediate group, with a reading of 71 ml. per minute in Case 36. Clearances of the order of 20 to 80 ml. per minute only were found in eight of the 31 thyrotoxic persons in whom the calculation was possible; in all except one (Case 73) of these eight patients the toxicity was of Grades 1 and 2. The remaining thyrotoxic cases all had clearances in excess of 80 ml. per minute, the value quoted by Pochin (1950) as being, in his experience, that below which Graves' disease is not probable. Keating, Wang, Luellen, Williams, Power, and McConahey (1949) quoted four cases of exophthalmic goitre with thyroid iodine clearance rates of less than 70 ml. per minute; we therefore agree with these workers that it is possible to find comparatively low clearance rates in the presence of thyrotoxicosis, and the absence of such low readings in the series of Myant, Pochin, and Goldie (1949) is

probably due to the absence of cases with only slight degrees of thyrotoxicosis. On the evidence of our series there appears not to be a clear-cut separation, but a gradual transition, between the thyrotoxic and the euthyroid individual. It can be seen that there is a tendency for the most severe cases to have the highest, and the mildest cases the lowest, thyroid clearance rates, and that rates higher than normal occur in a number of patients with anxiety state and non-toxic goitre. It is possibly significant that four of the eight cases of 'overlap' were cases

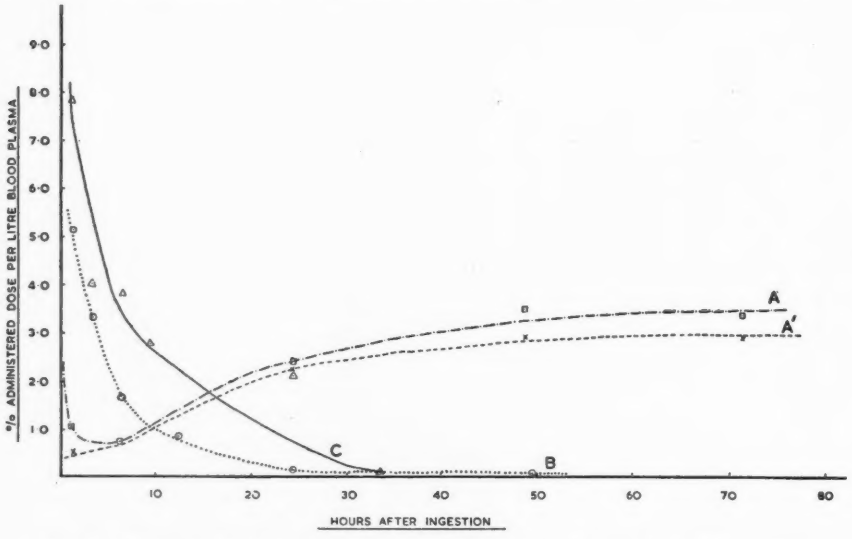

FIG. 7. Curves showing plasma activity in selected typical cases after administration of radioactive iodine. (By courtesy of *The British Journal of Radiology*.)

A = Total plasma activity (thyrotoxicosis).
A′ = Plasma protein-bound activity (thyrotoxicosis).
B = Total plasma activity (normal subject).
C = Total plasma activity (myxoedema).

of toxic adenoma rather than diffuse thyrotoxicosis, and that patients with toxic adenomata usually have clearance rates very considerably lower than those found in diffuse thyrotoxicosis. We feel that this is because the probably higher clearance rate of the hyperfunctioning adenoma is masked by the relatively normal rate of the rest of the gland. In this group of cases, therefore, estimations of the clearance rate resemble those of the gland uptake in their inability to indicate toxicity. They have, however, the advantage that they can be accurately calculated without knowledge of the actual dose given.

Plasma activity estimations. All the above results are indices of the capacity of the thyroid gland to concentrate iodide presented to it. Very soon after starting our work we felt that a more physiological measure of thyroid function would be an index of the ability of the thyroid to convert iodide into thyroxine and discharge it into the circulation. It therefore became necessary to determine at what time the most valuable diagnostic information could be obtained from

an observation of total plasma activity and of plasma activity due to iodine in protein-bound form. Preliminary work showed that after the initial rise in plasma concentration which follows absorption of the radioactive iodine there is a fall, which reflects the disappearance of radioactive iodine as iodide from the blood into the thyroid gland, urine, and other sites of disposal (Fig. 7). The rate of this disappearance of radioactive iodine from the blood reflects changes in thyroid function, being more rapid in thyrotoxicosis than in normal subjects, and less rapid in hypothyroidism. Blood estimations during this phase are of diagnostic value, and the suggestion of Myant and Pochin (1949), that the isolated observation of plasma activity two hours after administration of radioactive iodine is a valuable test, is based on the fact that the disappearance of iodine from the blood is very rapid in thyrotoxicosis. They noted that the plasma activity in normal persons was at this time always more, and in thyrotoxicosis less, than two per cent. of the administered dose per litre of plasma. In toxic cases, therefore, a minimal level of plasma activity is reached at an early stage, corresponding to the earlier peak of thyroid absorption, whereas normal function is characterized by a more prolonged and gradual fall in activity. The next phase of the curve of radioactive iodine concentration in the plasma indicates the appearance in the blood of iodine in protein-bound form, probably chiefly as thyroxine. This phase starts much earlier in thyrotoxic individuals than in normal persons; iodine in protein-bound form can occasionally be detected in thyrotoxic individuals at a very early stage (within two or three hours), and its continued discharge into the blood is shown by a marked secondary rise in the level of plasma activity. The rise is difficult to detect by present techniques in normal persons: in any case, it is of a much smaller degree, and it is most unusual to find more than a negligible amount of radioactive iodine in protein-bound form in a normal person before the third or fourth day. We therefore felt that 48 hours would be the best time at which to measure both the total plasma activity and that due to protein-bound iodine. Any activity then present should be due chiefly to protein-bound iodine in thyrotoxic patients; in normal persons activity should be minimal, because by that time the greater part of the administered dose should have been excreted in the urine, or held in the thyroid gland, from which the output of thyroxine would not yet be appreciable.

The results are shown in Figs. 8 and 9. An estimation of the total activity alone provided a rough separation between the toxic subjects and those with normal or intermediate thyroid function. The cases in the overlap zone were chiefly those with low clearance rates, and consequently with a more delayed absorption of circulating radioactive iodine by the gland. Nevertheless, there is almost a tenfold difference between the mean of 0·16 per cent. of the dose given per litre of plasma in the normal and intermediate groups combined, and the mean of 1·53 per cent. per litre in the toxic group. Values in excess of 0·7 per cent. per litre were usually found in thyrotoxicosis, and seldom, if ever, in euthyroid persons, but values smaller than 0·7 per cent. per litre were not incompatible with a diagnosis of thyrotoxicosis. When the protein-bound activity

was measured (Fig. 9) a very sharp demarcation became apparent between the toxic group on the one hand, and the intermediate and normal groups on the other. In the absence of toxicity only two patients showed a protein-bound activity in excess of 0·2 per cent. per litre, and 31 patients showed values less than 0·1 per cent. per litre. On the other hand, only two patients who had been

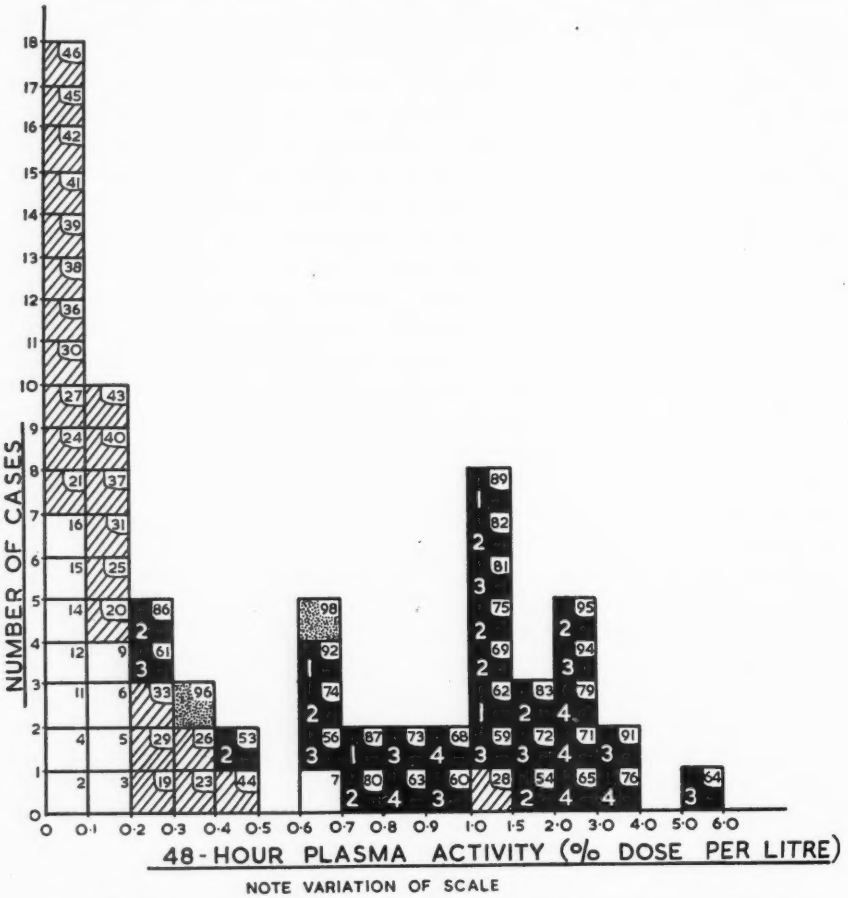

FIG. 8. Distribution of estimations of the total plasma activity 48 hours after a dose of radioactive iodine. (For explanation of symbols, see Fig. 1.)

definitely graded as thyrotoxic showed values less than 0·2 per cent. per litre, whereas all the remainder who were tested (24 cases) showed values in excess of 0·4 per cent. per litre. This test was therefore manifestly a useful diagnostic aid, and our experience suggests that, if a greater amount than 0·5 per cent. of the dose per litre of plasma is present at 48 hours in protein-bound form, the patient should be regarded as a case of thyrotoxicosis; values below this level are only occasionally found in the presence of thyroid overactivity. The higher amounts

of activity in protein-bound form were found in those patients who had a rapid fall in thyroid gland uptake after the peak value had been reached. These

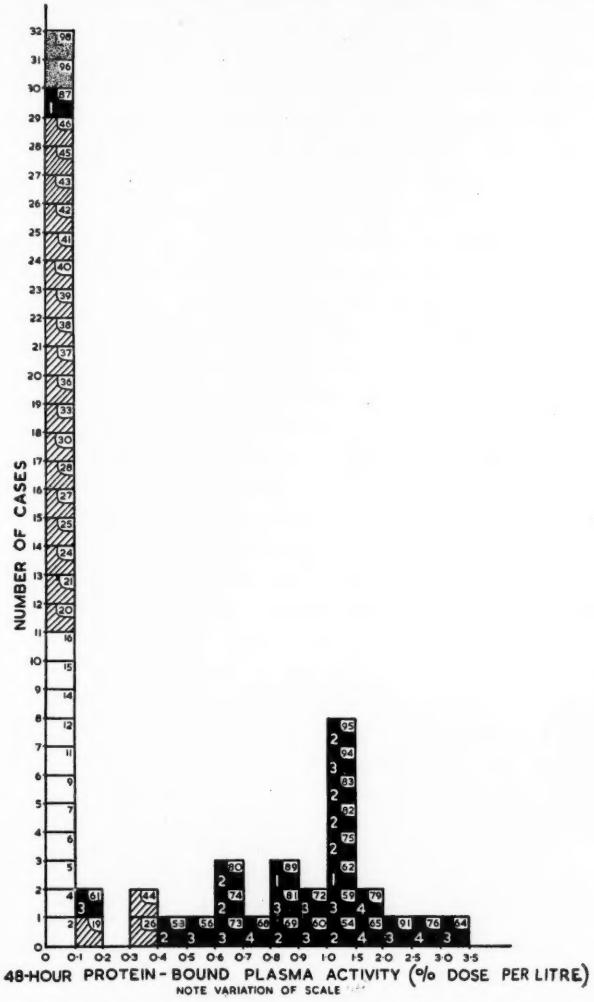
NUMBER OF CASES
0 0·1 0·2 0·3 0·4 0·5 0·6 0·7 0·8 0·9 1·0 1·5 2·0 2·5 3·0 3·5
48-HOUR PROTEIN-BOUND PLASMA ACTIVITY (% DOSE PER LITRE)
NOTE VARIATION OF SCALE

FIG. 9. Distribution of estimations of the protein-bound plasma activity 48 hours after a dose of radioactive iodine. (For explanation of symbols, see Fig. 1.)

results indicate a more rapid turnover of iodine, discharged as thyroxine (Cases 64, 65, 76, and 79).

While this work was in progress several observers reported somewhat similar observations; but they have usually chosen to make their observations 24 hours after the dose, and their work has centred upon a study either of the rate at which radioactive iodine becomes protein-bound or of the absolute amount

present. Clark, Moe, and Adams (1949) and Sheline and Clark (1950) found that patients in whom at 24 hours more than 50 per cent. of the total plasma activity was due to protein-bound iodine were thyrotoxic, a statement with which we could not disagree if the time were altered to 48 hours. They required doses of at least 50 to 200 microcuries of radioactive iodine for their observations. Freedberg, Ureles, and Hertz (1949) demonstrated that after 24 hours protein-bound radioactive iodine reached higher levels in thyrotoxic than in normal subjects; but they found that the total plasma activity at that time did not sharply separate toxic from normal thyroid function. Williams, Jaffe, and Bernstein (1949) also reported that in thyrotoxicosis the total and protein-bound iodine radioactivity was above normal after 24 hours, and they suggested, although they did not show, that a sharper separation might be achieved if longer intervals elapsed before the specimens were collected. McConahey, Keating, and Power (1949) noted that the levels of protein-bound radioactive iodine were higher in thyrotoxic than in euthyroid individuals. They also observed that in thyrotoxic subjects all the circulating radioactive iodine was protein-bound after a period which averaged 47 hours, but that in normal individuals the average time required was about four days. This finding re-emphasized the value of making observations of plasma activity after 48 hours, a time chosen by us as the result of continuing such observations over a period of time (Fig. 7). It should be emphasized that none of the above workers carried out estimations both of the thyroid uptake of radioactive iodine and of the plasma levels of protein-bound activity in the same individuals.

Discussion

The diagnosis of thyrotoxicosis can usually be made on the basis of history and physical examination alone. There are, however, many cases in which additional information is of great value; for example, the problem of overactivity of the gland is always raised if the patient has a goitre, and especially if there is also tachycardia. All patients who have had thyrotoxicosis in the past, and who have been treated, present difficulties in assessment. It is also well known that anxiety states may simulate thyroid disease. We have found the estimation of the blood-cholesterol of little value in hyperthyroid states, although it is of value in hypothyroidism. Our experience thus agrees with that of Peters and Man (1950) and of Bartels (1950). An estimation of the basal metabolic rate can be of value if done in hospital and in duplicate, but our figures show clearly its relative unreliability as a diagnostic method. Rapport and Curtis (1950) claimed that chemical estimation of the protein-bound iodine in the plasma is the best measure of thyroid function; we believe that this is probably the case, but feel that the technical difficulties involved in carrying out the determination accurately are much greater than in making observations with radioactive iodine. Such observations are not difficult to carry out, and where possible we would advise making the complete series described in the present paper. If, however, it is desired to make routine observations of a large

number of subjects, or to investigate them as out-patients, it becomes necessary to select one, or at the most two, of the tests.

An assessment of the total amount of radioactive iodine absorbed by the thyroid gland, or excreted by the urine, indicates the capacity of the thyroid gland to retain inorganic iodide. This capacity is known to be considerably influenced by previous administration of iodine or of drugs which have an effect on thyroid function, such as thiocyanate, the thiouracil group, or resorcinol (Bull and Fraser, 1950); furthermore, the capacity of the gland to retain iodine may alter considerably within a short time after administration of the drug is stopped. Nevertheless, the iodide-retaining capacity of the thyroid gland is very greatly increased in conditions in which there is clinical evidence of increased thyroid activity. Measurements of the degree and rate of iodide uptake therefore provide an index of thyroid activity which, in the majority of cases, separates persons with normal function from those with hyperthyroidism or with hypothyroidism. But the degree of overlap is such that we feel that the test is of less value in the difficult intermediate group of cases, in which there is a possibility either of mild hyperthyroidism or of a non-toxic goitre with a superimposed anxiety state. We therefore do not agree with Werner, Hamilton, Leifer, and Goodwin (1950) and Jaffe and Ottoman (1950), who found the uptake of radioactive iodine by the gland to be a sufficiently accurate index of disturbed function to merit its adoption as a routine test. Urinary excretion of radioactive iodine is subject to the same objections as gland uptake, with the added difficulties inherent in the collection of urine samples. It is also very much less suitable as a diagnostic procedure applicable to out-patients, and its only advantage is the relatively small dose of radioactive iodine necessary for its performance. Of the figures which give evidence of the speed of uptake of iodine by the gland the most useful are probably those of the thyroid clearance rate, but even here we agree with Keating, Wang, Luellen, Williams, Power, and McConahey (1949) that low clearances may occur in cases of undoubted thyrotoxicosis. Pochin (1950) has suggested a simple method of measuring the thyroid clearance rate by taking the ratio of counts obtained over the thyroid to counts obtained over the thigh one hour after a dose of radioactive iodine. This method, though simple, has the same defects as the measurement of clearance rates using the method which involves the taking of blood samples, and is less accurate.

The methods we have so far discussed give figures which are related to the iodine concentrating and retaining capacity of the thyroid gland. The measurements we shall next consider are related to the amount of circulating thyroxine, and appear *a priori* more likely to give figures corresponding to deviations of the individual from normal thyroid function. This we find in fact to be the case. The total plasma activity correlates well, and the protein-bound activity very well, with the clinical assessment of patients. The most striking difference between these results and those obtained by all the other methods of assessment with radioactive iodine is that nearly all our intermediate group of patients fall into the normal range. It will be remembered that the patients in this group

did not, in fact, show clinical signs of thyrotoxicosis, and that their tendency in the other tests to give results intermediate between the normal and toxic groups was not always easy to explain. There is no doubt that the protein-bound activity of the plasma 48 hours after the administration of a dose of radioactive iodine is the measurement which best separates the clinically toxic from the non-toxic group of patients. The sensitivity of the test is not at present such that measurements of the 48-hour protein-bound plasma activity can differentiate between patients in the normal and intermediate groups. There is a slight difference between the two groups if mean uptake figures are

TABLE V

Atypical Results

Case number	*Sex*	*Age (years)*	*Diagnosis*	*Basal metabolic rate (%)*	*Peak gland uptake (% dose)*	*Time to ½ peak uptake (mins.)*	*24-hour urine excretion (% dose)*	*Thyroid clearance rate (ml./min.)*	*48-hr. protein-bound plasma activity (% dose/litre)*
Intermediate group:									
19	F	45	Non-toxic goitre	+36	46	132	32	44	0·15
26	F	63	Burnt-out thyrotoxicosis	−27	47	410	54	18	0·4
44	F	33	Treated thyrotoxicosis. Anxiety state	−3	56	108	32	60	0·35
Toxic group:									
61	M	34	Thyrotoxicosis, Grade 3	+59	72	96	21	150	0·13
87	F	52	Toxic adenoma, Grade 1	..	60	136	21	84	negligible

compared (Table IV), and this is not reflected in the estimations of protein-bound activity. We believe that with improved counting technique it may be possible, with the dosage used in the present study, to demonstrate that there is in fact a gradation of protein-bound plasma activity at 48 hours throughout the intermediate group. It is understandable that a patient who has had a thyroidectomy, and presents clinical symptoms suggestive of thyrotoxicosis, should have some slight disturbance of thyroid function, even if it is not of sufficient degree to constitute frank thyrotoxicosis. The results of the present study have shown that the presence of the clinical manifestations of thyrotoxicosis, as assessed by us, is associated with a protein-bound plasma activity at 48 hours which usually exceeds 0·4 per cent. per litre, but with improvements in counting technique we anticipate that it will become possible to separate lesser degrees of abnormality of thyroid function. We may thus hope to distinguish between truly normal persons and certain members of our intermediate group. Such a separation is likely to appear in the zone extending from 0 to 0·2 per cent. per litre. The few cases which gave anomalous results with this test must now be considered, and the relevant information has been collected in Table V. Case 87 showed results in all the tests which fell into the 'overlap' group, and

it is possible that this patient, clinically assessed as Grade 1, was in fact not suffering from thyrotoxicosis. Case 61 fell into the toxic group both clinically (Grade 3) and in respect of peak gland uptake, time to half-peak, and clearance rate. There may well have been an error in the assay of protein-bound activity in this instance. Little help is obtained from the other investigations in Cases 19, 44, and 26, which all fell into the 'overlap' region. When it is considered that in Fig. 9 there are two possible errors in the placing of cases—an error in clinical assessment and a failure in accurate radiochemical assay—it is remarkable that the correlation is so satisfactory. With regard to the accuracy of the technique at the levels of radioactivity present in the anomalous cases, it is unlikely that any error in counting would be sufficient to make a difference of more than 0·1 per cent. in the estimated activity. Any case classified in the 0·1 to 0·2 per cent. column is not therefore misplaced by more than one column, and cannot be regarded as assignable to any other than the 0 to 0·1 per cent. or 0·2 to 0·3 per cent. columns.

An estimation of plasma protein-bound activity has several further advantages over values dependent upon the study of iodine uptake. It can be seen from Tables II (*a*) and II (*b*) that it provides a positive index of toxicity which agrees with the clinical diagnosis in many cases which give equivocal results by the other techniques. When a case was really difficult to classify clinically, we found subsequently that the iodine uptake figures and clearance rates were equally unhelpful. The estimation of protein-bound plasma activity at 48 hours, being a functional index of circulating thyroid hormone, and quite separate from other indices measuring iodide uptake, appears to assist in the further classification of these difficult cases, for in many of them it is the only index which agrees with the ultimate clinical diagnosis, frequently only reached after many months. It has also been our experience, in agreement with other workers, that recent administration of iodine-containing compounds, especially those used for diagnostic radiological procedures such as cholecystography, may very greatly depress iodine uptake, and render a radioactive iodine test invalid. But in two patients not included in the present series, who clinically were frankly toxic, we found a raised 48-hour protein-bound activity in the plasma although the gland uptake was normal; both patients had recently received iodine, one in the form of an organic compound given for cholecystography four weeks previously, and the other in large doses of inorganic iodine given within the previous three weeks. Keating, Haines, Power, and Williams (1950) found that the depressant effect of iodide seldom lasted longer than two weeks, but that a cholecystogram might depress the gland uptake of iodine for many months. Furthermore, Myant, Pochin, and Goldie (1949) have shown that the rate of renal excretion of iodide is proportional to the plasma concentration of radioactive iodine, and the renal clearance rate has the same value in normal and in thyrotoxic subjects (Pochin, 1950). In the presence of renal disease, however, when renal excretion of the isotope is delayed, there may be an abnormally high uptake of radioactive iodine into the thyroid gland, possibly giving the impression of thyroid overactivity. In such circumstances there is no rise in the total or protein-bound

plasma activity at 48 hours, and toxicity is not suggested by this test. There is an important reservation to be made in interpreting estimations of plasma protein-bound radioactivity. Blomfield, Jones, Macgregor, Miller, and Wayne (1951) have shown that it is possible to get abnormal results in patients who have been treated, and who no longer show any clinical evidence of toxicity. In such cases there appears to be a delay in the return of the protein-bound plasma activity to normal after successful treatment, and clinical cure precedes the objective evidence of normal thyroid function provided by the test. Rall (1950) has demonstrated that in some cases of thyroid disease a significant amount of activity may be present in the di-iodotyrosine fraction of the protein-bound iodine in the plasma. We are now attempting a separation of the thyroxine and di-iodotyrosine fractions, which may help to explain some of the anomalous results following treatment. It is our opinion, nevertheless, that if a single easily performed test of thyroid function is required, the estimation of the protein-bound plasma activity 48 hours after the administration of radioactive iodine gives the most valuable diagnostic information, and is suitable as a screening procedure for out-patients.

Our primary aim in this investigation has been to find a simple objective test for the presence of thyrotoxicosis. We have not made a detailed attempt to differentiate between the mechanism of primary thyrotoxicosis and that of thyrotoxicosis secondary to previously existing adenomata or nodular goitres. The two groups of cases are roughly separated in Tables II (*a*) and II (*b*), and the means of the results of investigations in these two groups have been separately presented in Table IV. The metabolism of radioactive iodine appears to be very similar in both groups, but we have no evidence that it is identical.

It should be realized that no routine test of a single thyroid function is by itself adequate to establish the existence of abnormal thyroid activity. Werner, Hamilton, Leifer, and Goodwin (1950) claimed that determinations of the gland uptake of radioactive iodine and the basal metabolic rate, combined with the chemical estimation of protein-bound iodine, gives 95 per cent. accuracy in the assessment of thyroid function. With regard to the use of radioactive iodine, we feel that if the necessary equipment is to be obtained and used, it is worth while investigating every patient as fully as possible. From such a study of the different aspects of thyroid function the most accurate deductions can be drawn regarding the degree of over- or under-activity of the gland. There will always be patients about whose thyroid function the clinician remains in doubt even after the fullest clinical and laboratory investigation. If their iodine metabolism is investigated by the isotope technique valuable additional information is obtained, and great reliance can be placed on the results. The accuracy of the final diagnosis, with its therapeutic and prognostic implications, is thereby greatly enhanced.

Acknowledgements

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Summary

1. Radioactive iodine has been used to investigate the thyroid function of a group of 16 normal subjects, 30 patients in an 'intermediate' group with non-toxic goitres, treated thyrotoxicosis, or anxiety states, 44 patients with thyrotoxicosis or toxic adenomata, four patients with myxoedema, one with acromegaly, and one with Hashimoto's thyroiditis.

2. The metabolism of orally administered radioactive iodine has been studied in each group with respect to the rate and degree of uptake of the isotope by the thyroid gland, the urinary excretion in the first 24 hours, the thyroid clearance rate of iodide from the plasma, and the amount of activity due to the isotope found in the plasma 48 hours after the dose was given. The proportion of the plasma activity which was due to radioactive iodine in protein-bound form has been estimated.

3. Characteristic patterns of behaviour of the administered iodine were found for each group in respect of each criterion investigated. The gland uptake at its peak value showed a range of 21 to 54 per cent. with a mean of 38 per cent. in the normal group, 24 to 69 per cent. with a mean of 48 per cent. in the intermediate group, and 56 to 92 per cent. with a mean of 74 per cent. in the toxic group. The uptake in the myxoedematous patients ranged from 4 to 23 per cent. Gland uptakes at 24 hours showed similar ranges, but there was more overlap between the toxic group and the intermediate and normal groups.

4. The time was measured to the moment at which the thyroid gland had absorbed half the iodine retained at the peak point of the curve. A time to half-peak in excess of 160 minutes was characteristic of normal thyroid function, and values below 100 minutes were characteristic of thyrotoxicosis. Intermediate times occurred both in clinically normal and in thyrotoxic subjects.

5. Thyroid iodide clearance rates in normal persons were commonly below 50 ml. per minute, and usually well above 80 ml. per minute in the presence of clinical thyrotoxicosis, but intermediate values were found in non-toxic goitre, treated thyrotoxicosis, anxiety states, and the milder degrees of thyrotoxicosis.

6. The 24-hour urinary excretion of the isotope showed that excretions of under 20 per cent. of the dose were usual with clinical evidence of toxicity, and excretions of over 35 per cent. with normal function. Intermediate excretions were found both in mild thyrotoxicosis and in non-toxic goitre.

7. Tests which measured the rate and degree of iodide concentration in the thyroid gland showed a rough correlation with the clinical severity of the disease.

8. Estimation of the protein-bound plasma activity 48 hours after administration of the dose showed a very sharp division between normal and thyrotoxic subjects. Values in excess of 0·4 per cent. of the dose per litre of plasma were

found in thyrotoxicosis, and values below 0·1 per cent. were found in non-toxic goitres, treated thyrotoxicosis, anxiety states, and normal subjects. Estimations of the total plasma activity at 48 hours provided valuable but less definite diagnostic data, values in excess of 0·7 per cent. per litre being usually found in thyrotoxicosis, and seldom found in euthyroid persons.

9. The estimation of the protein-bound plasma activity 48 hours after a tracer dose of radioactive iodine is essentially a measure of the amount of circulating thyroxine. It gives valuable diagnostic information, and is suitable as a screening procedure for out-patients.

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THE INFLUENCE OF INTRAVENOUS DIGOXIN ON RENAL FUNCTION IN CONGESTIVE CARDIAC FAILURE[1]

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The value of the foxglove as a diuretic in dropsy was first recognized by William Withering in 1785. Since that time the digitalis glucosides have come to assume the primary therapeutic role in the treatment of congestive cardiac failure, and their pharmacological action upon the mammalian heart has been the subject of extensive studies. Cushny (1925), Schäfer (1934), Cattell and Gold (1938), and Gold and Cattell (1940), employing heart-muscle strips, isolated hearts, and heart-lung preparations, showed that digitalis increases the force of the myocardial contraction, and Peters and Visscher (1936), in metabolic studies of the isolated heart, showed that it can increase the efficiency as well as the force of the myocardial contraction. The slowing of the heart-rate which follows digitalization both in man and in animals has been found to be due in part to vagal stimulation, and therefore abolished by atropine, and in part to depression of atrio-ventricular conduction—an observation which we owe to the electrocardiographic studies of Lewis, Drury, and Iliescu (1921–2). The mode of action of digitalis upon the failing human heart has been a subject of renewed interest since the technique of right heart catheterization has made possible the measurement of the cardiac output and intracardiac pressures. The intravenous administration of the cardiac glucosides digoxin, lanatoside C, and ouabain to subjects with congestive heart failure is shortly followed by a significant augmentation of the cardiac output (McMichael and Sharpey-Schafer, 1944; Bloomfield, Lauson, Cournand, Breed, and Richards, 1946; Stead, Warren, and Brannon, 1948; Ferrer, Harvey, Cathcart, Webster, Richards, and Cournand, 1950). McMichael and Sharpey-Schafer observed that the augmentation of the cardiac output was usually accompanied by a reduction of the right auricular and systemic venous pressures, and concluded that the beneficial action of digoxin was due to a primary alteration of the venomotor tone, which relieved the load on the right heart in a manner similar to venesection or venous occlusion of the thighs. Further and more detailed studies by Bayliss, Etheridge, Hyman, Kelly, McMichael, and Reid (1950) have shown that the therapeutic action of digoxin in congestive heart failure is primarily upon the failing myocardium. Employing Homer Smith's renal clearance technique (Smith, Goldring, and Chasis, 1938), Merrill (1946) and Mokotoff, Ross, and Leiter (1948) studied renal function in congestive cardiac failure, and showed that the renal

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fraction of the cardiac output is greatly reduced, the glomerular filtration rate falls to a lesser extent, and the filtration fraction is abnormally high in such cases. These findings have been offered in support of the hypothesis of Warren and Stead (1944) that diminished renal blood-flow, due to an inadequate cardiac output, is responsible for the retention of salt and water; increased blood-volume and elevation of the systemic venous pressure are thus considered to be a secondary manifestation of the reduced renal blood-flow. Winton (1937) and Blake, Wégria, Keating, and Ward (1949) observed an enhanced tubular reabsorption of water and electrolytes in mammalian kidneys during constriction of the renal vein. Increased renal venous pressure has been postulated by Maxwell, Breed, and Schwartz (1950) as an additional factor which reduces the renal blood-flow and glomerular filtration in congestive cardiac failure. The purpose of the present investigation was to study the effects of intravenous digoxin upon renal function and systemic venous pressure in untreated subjects suffering from congestive cardiac failure of rheumatic, hypertensive, or ischaemic origin, and to compare its action with that of venous occlusion of the thighs, which is an alternative method of reducing systemic venous pressure.

Material and Methods

Renal function was assessed by measurement of the urinary clearance of diodone and inulin. Thirty-two subjects were studied. Fifteen of these—ten medical patients suffering from miscellaneous conditions other than heart failure, and five patients with cardiac disease who had responded satisfactorily to treatment—served as controls to determine the variation in consecutive clearance periods to be expected with the technique employed. Cases of cardiac failure secondary to thyrotoxicosis or chronic pulmonary disease, and patients with obvious renal disease or active reheumatic infection, were excluded from the series. All the subjects received one to two pints of water to drink before the investigation. None of the untreated cardiac patients had received mercurial or other diuretics beforehand. Cardiac patients with orthopnoea were investigated with the head and shoulders raised. The renal plasma-flow (clearance of diodone) and glomerular filtration rate (clearance of inulin) were determined by the technique described by Goldring and Chasis (1944). Priming and maintenance solutions of diodone and inulin were made up in suitable concentration in distilled water. The maintenance solution was given by continuous intravenous infusion at a rate of 2·0 ml. per minute. Thirty minutes were allowed for equilibration between plasma and extracellular fluid. Renal extraction of diodone was presumed to be complete at the plasma level maintained. The observed values for renal plasma-flow would be erroneously low, and those for the filtration fraction erroneously high, if the actual extraction ratio were significantly below this ideal level. Provided that the ratio remained constant for each subject during the period of the investigation, the observed variation in these two functions would not be affected by this inaccuracy. Blood samples were obtained from a peripheral vein at 30-minute intervals. Urine collections were made at 10- to 20-minute intervals through a many-holed indwelling catheter. The

bladder was washed out twice with sterile distilled water (50 ml. in all), and complete evacuation was obtained by injection of air, at the end of each collection period. The diodone and inulin in plasma and urine were determined by modifications of the methods of Alpert (1941) and Steinitz (1938) respectively. The filtration fraction was obtained from the ratio $\frac{C_{inulin}}{C_{diodone}} \times 100$; tubular reabsorption of water was calculated from the inulin U/P ratio. The systemic venous pressure was measured by a water manometer connected through a three-way tap to the 18-gauge infusion needle, which was placed in the median cubital vein. The venous pressure was referred to the horizontal plane passing through a point 5·0 cm. dorsal to the fourth costochondral junction. Digoxin (Burroughs Wellcome 'hypoloid'), in a dosage of 1·5 mg. dissolved in 10 ml. of normal saline, was administered into a peripheral arm vein. Venous occlusion of the thighs was obtained with two sphygomanometer cuffs maintained at the diastolic blood-pressure for periods of 10 to 20 minutes. Since the purpose of the investigation was to observe variations in renal function, and not the determination of absolute values, haematocrit readings were not made, nor were the values referred to the surface area of the subject under investigation.

Results

1. *Expected variation between consecutive clearance periods*

The renal plasma-flow and glomerular filtration rate were estimated in three consecutive periods in 12 control subjects without cardiac disease, and the values obtained for these two functions varied considerably from case to case. For this reason the variation of single observations from the mean value obtained in each subject was expressed as a percentage of the mean value. In this series the average standard deviation was 5·57 per cent. for the renal plasma-flow, and 5·12 per cent. for the glomerular filtration rate. The standard deviation of the third period from the mean of the first two was 6·82 per cent. for the renal plasma-flow, and 7·16 per cent. for the glomerular filtration rate. On the basis of these findings a deviation of $\pm$20 per cent. from the mean of the control periods after the administration of digoxin or venous occlusion of the thighs was considered to be significant.

2. *Renal function in untreated congestive cardiac failure*

This was studied in 12 subjects in whom failure was due to rheumatic, hypertensive, or ischaemic heart disease. Ten of the patients had a regular rhythm, and two had auricular fibrillation. In addition two had clinical evidence of aortic stenosis of a senile type. The findings are shown in Tables I and II, subdivision (*a*). In this series the mean renal plasma-flow was 234$\pm$23 ml. per minute, and the mean glomerular filtration rate was 72$\pm$6 ml. per minute; the mean value of the filtration fraction was 30·92$\pm$1·92 per cent. The tubular reabsorption of water as measured by the inulin U/P ratio varied widely, ranging between 137 and 12. The urine flow was below 2·0 ml. per minute in 10 of the 12 cases.

TABLE I

Influence of Intravenous Digoxin on Systemic Venous Pressure and Renal Function

(*a*) Before digoxin. (*b*) 30 to 40 minutes after digoxin

Case number	*Age (years)*	*Sex*	*Diagnosis*		*Systemic venous pressure (cm. saline)*	*Renal plasma-flow (ml./min.)*	*Glomerular filtration rate (ml./min.)*	*Filtration fraction (per cent.)*	*Inulin U/P ratio*	*Urine flow (ml./min.)*
1	67	M	H.H.D., R.R.	(*a*)	22·5	216	64	29·6	54	1·2
				(*b*)	12·0	425	123	28·9	27	4·5
2	58	M	I.H.D., R.R.	(*a*)	23·5	227	55	24·2	137	0·4
				(*b*)	17·0	309	75	24·2	75	1·0
3	56	M	I.H.D., R.R.	(*a*)	21·5	141	35	24·8	27	1·3
				(*b*)	15·0	240	53	22·1	16	3·3
4	53	M	I.H.D., R.R.	(*a*)	16·5	136	51	37·5	76	0·5
				(*b*)	9·5	180	66	36·6	29	2·3
5	36	M	R.H.D., R.R.	(*a*)	18·0	266	90	33·8	100	0·9
				(*b*)	16·0	303	92	30·4	77	1·2
6	66	M	I.H.D., A.S., R.R.	(*a*)	20·0	307	82	26·7	103	0·8
				(*b*)	20·0	215	73	33·9	91	0·8
7	21	F	R.H.D., R.R.	(*a*)	21·0	247	78	31·6	12	6·5
				(*b*)	21·0	252	72	28·6	11	6·3

Abbreviations in this and the following Tables: H.H.D. = hypertensive heart disease; I.H.D. = ischaemic heart disease; R.H.D. = rheumatic heart disease; A.S. = aortic stenosis; R.R. = regular rhythm; A.F. = auricular fibrillation.

TABLE II

Influence of Venous Occlusion Thigh Cuffs on Systemic Venous Pressure and Renal Function

(*a*) Before occlusion. (*b*) Maximum clearances observed during or immediately after occlusion

Case number	*Age (years)*	*Sex*	*Diagnosis*		*Systemic venous pressure (cm. saline)*	*Renal plasma-flow (ml./min.)*	*Glomerular filtration rate (ml./min.)*	*Filtration fraction (per cent.)*	*Inulin U/P ratio*	*Urine flow (ml./min.)*
8	53	F	R.H.D., A.F.	(*a*)	15·0	146	48	32·9	80	0·6
				(*b*)	14·0	152	53	34·8	88	0·6
9	63	M	I.H.D.	(*a*)	13·0	441	126	28·6	13	9·6
				(*b*)	9·0	497	127	25·5	13	9·9
10	62	M	I.H.D., A.S., R.R.	(*a*)	10·0	213	45	21·1	26	1·7
				(*b*)	5·0	219	40	18·3	19	2·1
11	48	M	R.H.D., A.F.	(*a*)	28·0	217	101	46·6	63	1·6
				(*b*)	22·0	236	110	46·6	38	2·9
12	52	M	H.H.D., R.R.	(*a*)	10·0	252	91	36·1	76	1·2
				(*b*)	5·0	274	84	30·6	60	1·4

3. *Renal function in treated congestive cardiac failure*

This was studied in five subjects whose cardiac failure had responded satisfactorily to rest in bed, digitalis, and mercurial diuretics, whose systemic venous pressure had returned to normal, and whose oedema had decreased or disappeared. The findings are shown in Table III. In this series the mean renal plasma-flow was 326±56 ml. per minute, and the mean glomerular filtration rate 77±12 ml. per minute. The mean filtration fraction for the group was 23·6

TABLE III

Renal Function in Treated Congestive Cardiac Failure when the Systemic Venous Pressure had Returned to Normal

Case number	*Age (years)*	*Sex*	*Diagnosis*	*Renal plasma-flow (ml./min.)*	*Glomerular filtration rate (ml./min.)*	*Filtration fraction (per cent.)*	*Inulin U/P ratio*	*Urine flow (ml./min.)*
13	67	M	H.H.D., R.R.	320	42	13·1	60	0·7
14	50	M	R.H.D. A.F.	293	89	30·4	74	1·2
15	47	M	R.H.D., A.F.	226	55	24·3	7	8·0
16	54	M	H.H.D., R.R.	589	118	20·2	65	1·8
17	31	F	R.H.D.	207	82	39·6	17	4·9

per cent., but covered a wide range between 39 and 13 per cent. The urine flow exceeded 2·0 ml. per minute in two of the five subjects; in one case, with a renal plasma-flow of 226 ml. per minute and a glomerular filtration rate of 55 ml. per minute, the urine flow averaged 8·0 ml. per minute; in another, with a renal plasma-flow of only 207 ml. per minute and a glomerular filtration rate of 82 ml. per minute, the urine flow averaged 4·9 ml. per minute.

4. *Influence of intravenous digoxin upon the systemic venous pressure and renal function*

Seven subjects with untreated congestive cardiac failure were studied. Two additional cases have not been included owing to coexisting severe renal disease. The systemic venous pressure and measurements of renal function before, and 30 to 40 minutes after, 1·5 mg. of intravenous digoxin are shown in Table I.

Systemic venous pressure. In four subjects there was a marked reduction in systemic venous pressure, the maximum fall observed ranging between 10·5 and 6·5 cm. of water. In one subject a fall of only 2·0 cm. was observed, and in two cases the pressure remained unchanged.

Renal function. In the four subjects who showed a marked fall in systemic venous pressure there was a significant increase in renal plasma-flow and glomerular filtration rate. The increase in renal plasma-flow above the control

period varied from 96 per cent. in Case 1 to 32 per cent. in Case 4, and the increase of the glomerular filtration rate showed a range of 90 to 28 per cent. Although the subject with the maximum fall in venous pressure showed the greatest increase in the measurements of renal function, there was no obvious correlation between the two values. The filtration fraction fell slightly in three of these

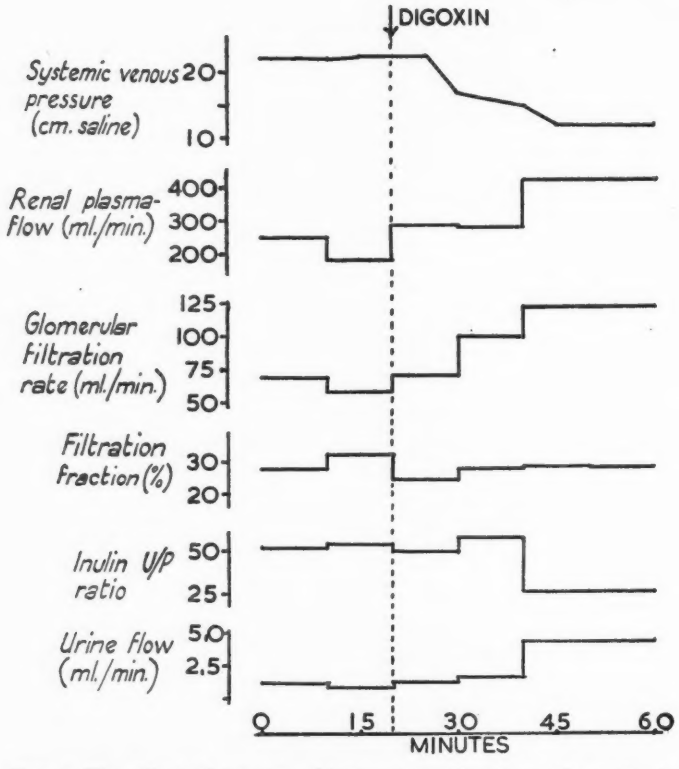

FIG. 1. The effect of 1·5 mg. of intravenous digoxin on the systemic venous pressure and renal function in Case 1.

patients, and remained constant in one. In one subject (Case 5) a small reduction in systemic venous pressure of 2·0 cm. was accompanied by an insignificant increase in renal plasma-flow and glomerular filtration. In one subject (Case 7) both systemic venous pressure and renal function were unchanged by digoxin during the period of observation. In one subject (Case 6) with ischaemic heart disease and aortic stenosis, the venous pressure remained unchanged, but the renal plasma-flow fell by 30 per cent. and the filtration fraction rose from 26·7 to 33·9 per cent.

Urine flow. In Cases 1 to 4 the urine flow increased, the maximum rise observed ranging between 4·6 and 2·5 times that of the control period. An increased glomerular filtration rate and diminished tubular reabsorption of water both

played a part in determining this rise; the mean inulin U/P ratio in these four cases fell from 73·4 before digoxin to 36·8 after digoxin. In Case 5 there was a slight increase in urine flow and a slight fall in the inulin U/P ratio. Cases 6 and 7 showed no change.

Fig. 1 shows the continuous observations of systemic venous pressure and

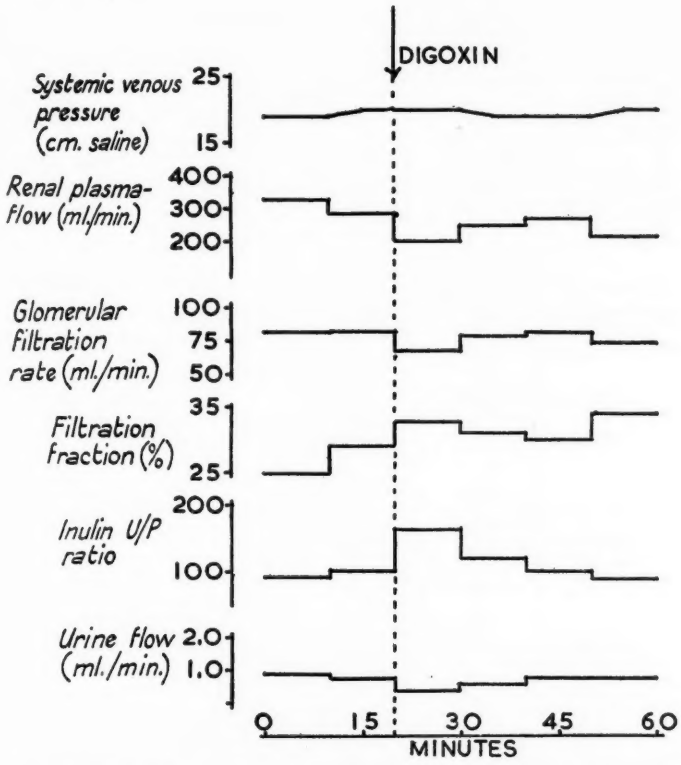

FIG. 2. The effect of 1·5 mg. of intravenous digoxin on the systemic venous pressure and renal function in Case 6.

renal function before and after digoxin in Case 1. It will be observed that the fall in venous pressure preceded any alteration in renal function, and that the renal plasma-flow, glomerular filtration rate, and urine flow rose simultaneously. Fig. 2 shows similar observations in Case 6. The venous pressure remained unchanged after digoxin, there was a transient depression of renal function immediately after its administration, and while the glomerular filtration rate and urine flow tended to return to the control values the renal plasma-flow remained significantly depressed, and the filtration fraction rose.

Control group. The influence of intravenous digoxin upon the systemic venous pressure and renal function was observed in five subjects without cardiac disease. In four of these subjects there was no significant alteration in the

systemic venous pressure, and the maximum observed variation in the renal plasma-flow and glomerular filtration rate were within ±12 per cent. of the control observations. Fig. 3 shows the influence of digoxin upon a subject of 46 years with a prolapsed intervertebral disk. The increase in urine flow was attributed to water ingestion, and it will be noted that this diuresis had begun

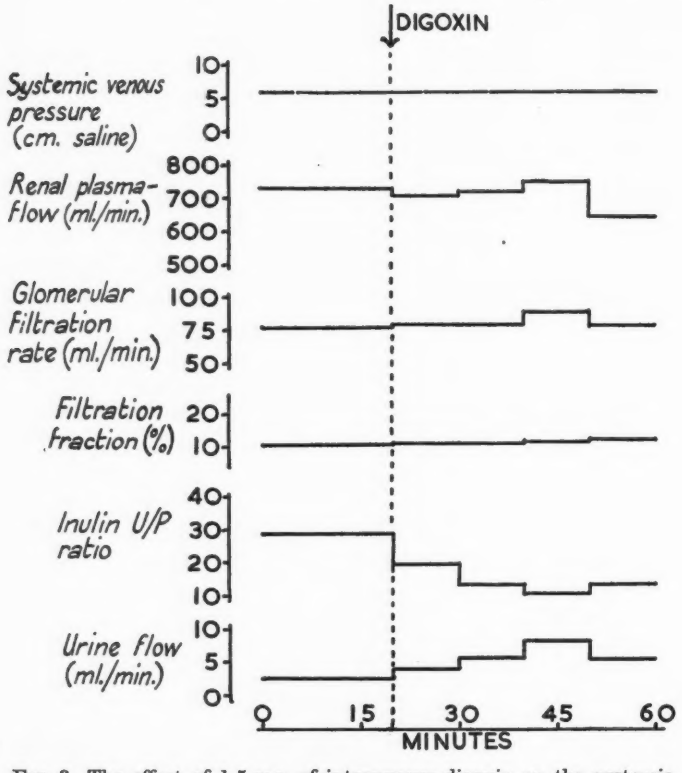

FIG. 3. The effect of 1·5 mg. of intravenous digoxin on the systemic venous pressure and renal function in a subject without cardiac or renal disease.

to fall during the period of observation. One subject, a woman with essential hypertension, showed marked toxic symptoms 10 minutes after the administration of digoxin, with bradycardia, sweating, nausea, and vomiting. These symptoms were accompanied by marked depression of the renal plasma-flow and glomerular filtration rate, with oliguria, which slowly recovered during the next 30 minutes.

5. *The influence of venous occlusion thigh cuffs upon the systemic venous pressure and renal function*

Five subjects with untreated congestive cardiac failure were studied. The systemic venous pressure and renal function before, and the maximum changes

observed during or immediately after, venous occlusion of the thighs are shown in Table II.

Systemic venous pressure. In four subjects there was a marked reduction in the systemic venous pressure, the maximum fall obtained ranging between 6·0 and 4·0 cm. of water, and occurring five to ten minutes after the initial inflation

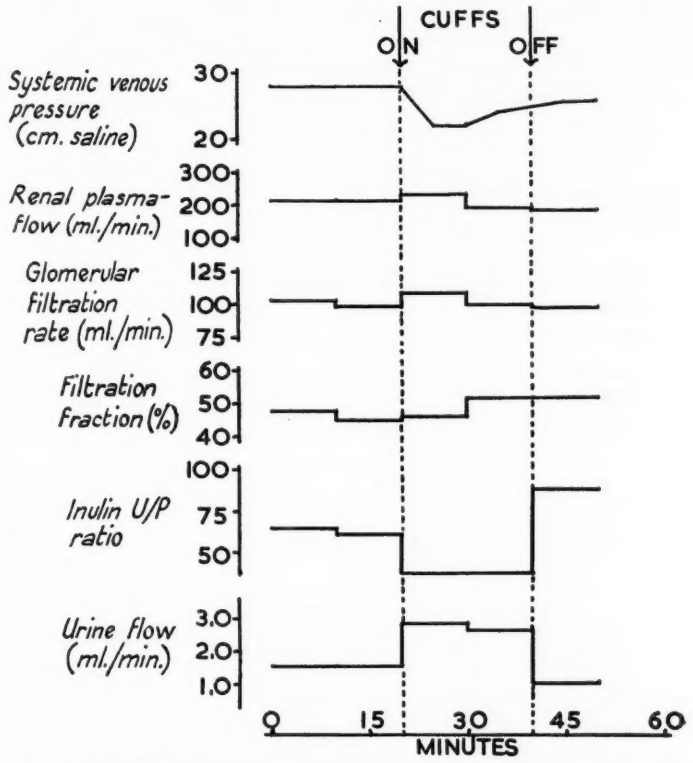

FIG. 4. The effect of venous occlusion thigh cuffs on the systemic venous pressure and renal function in Case 11.

of the cuffs. In one subject (Case 8) a maximum fall of only 1·0 cm. of water was obtained.

Renal function. None of the subjects showed a significant alteration of the renal plasma-flow or glomerular filtration rate during or immediately after venous occlusion of the thighs. The maximum observed variation lay within ± 13 per cent. of the value found in the control periods.

Urine flow. In four subjects there was no significant alteration in the urine flow. In one subject (Case 11) who showed the maximum fall in systemic venous pressure in this group (from 28·0 to 22·0 cm. of water) there was a transient but significant increase in urine flow during the period of venous occlusion of the thighs. During the control periods in this case the inulin U/P ratio averaged

63·2, and it fell to 37·8 during the period of venous occlusion, rising to 89·1 when the cuffs were released and the systemic venous pressure rose towards its former level. Fig. 4 shows the continuous observations made upon this patient. Fig. 5 shows the continuous observations in Case 8; it will be seen that no significant alterations in renal function or urine flow were produced by venous occlusion of the thighs.

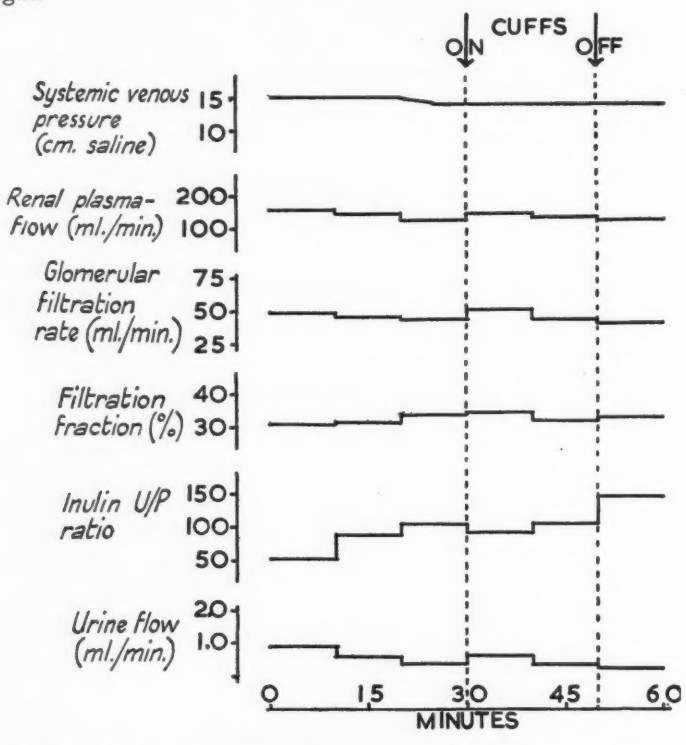

FIG. 5. The effect of venous occlusion thigh cuffs on the systemic venous pressure and renal function in Case 8.

Discussion

Renal function in congestive cardiac failure. The depression of the renal plasma-flow and glomerular filtration rate, and increase of the filtration fraction, observed in cases of untreated congestive cardiac failure in the present investigation, are in agreement with the findings of other workers (Merrill, 1946; Mokotoff, Ross, and Leiter, 1948; Brod and Fejfar, 1950). Personal observations of the renal plasma-flow of subjects resting in bed, without clinical evidence of cardiac or renal disease, have shown that it varies widely between 750 and 350 ml. per minute, although the figure is rarely below 700 ml. per minute in healthy young men. It would therefore be hazardous to speculate upon the degree to which the renal plasma-flow is reduced by cardiac failure where the

resting value before failure is unknown. Comparison of the mean glomerular filtration rate in the group of patients with untreated cardiac failure with the mean value obtained in those who were responding satisfactorily to treatment shows a difference of only 5 ml. per minute (72 and 77 ml. per minute respectively). It is therefore difficult to correlate the improved clinical state with an increase in the glomerular filtration rate at rest. In conformity with these findings Bradley and Blake (1949) have pointed out that the glomerular filtration rate in many patients recovering from cardiac failure fails to show a significant increase, and in a few may actually fall. The mean value for the renal plasma-flow was substantially greater in the treated patients than in the untreated patients in the present series, but two subjects (Cases 15 and 17, Table III) who were making a satisfactory recovery, with loss of oedema and normal venous pressures, had a very low renal plasma-flow. The tubular reabsorption of water as measured by the inulin U/P ratio varied widely, without significant trends, in both treated and untreated patients.

The influence of intravenous digoxin upon renal function. The diuresis induced by digoxin in four of the seven subjects studied occurred within 40 minutes of the administration of the drug, and was preceded in each case by a substantial reduction of the systemic venous pressure; it was accompanied by a significant increase in the renal plasma-flow and glomerular filtration rate, and by a diminution in the tubular reabsorption of water. In the absence of toxic manifestations, digoxin in the same dosage failed to influence the renal function of subjects without cardiac failure. This observation is in accord with therapeutic experience of the drug. The knowledge that digoxin augments the output of the failing heart makes it difficult to escape from the conclusion that the increase in renal plasma-flow and glomerular filtration rate observed in these cases reflects an increase in cardiac output. The insignificant change in the filtration fraction indicates that the improvement in renal plasma-flow is not accompanied by any great alteration in the relative tone of the afferent and efferent glomerular arterioles. Lacking simultaneous measurement of the change in cardiac output produced by the drug, we cannot say whether the rise in the renal plasma-flow is merely a passive response to an increase in cardiac output or whether an increase in the renal fraction of the total blood-flow plays a part in its production. The increase in the renal plasma-flow observed in our patients was of the same order as the rise in the resting cardiac output observed by McMichael and Sharpey-Schafer (1944) in cases of cardiac failure after administration of digoxin. It will be noticed that the improvement in renal function after digoxin was preceded in each case by a significant fall in the systemic venous pressure. Although Merrill (1946) was unable to find any correlation between the depression of renal plasma-flow and the height of the systemic venous or right auricular pressure in chronic congestive failure, Maxwell, Breed, and Schwartz (1950) have suggested that an increase in the renal venous pressure is an additional factor which is responsible for the depressed renal function in some sufferers from that condition. The authors' personal observations have shown that an increased urine flow after the administration of digoxin is invariably

associated with a rise in the rate of glomerular filtration, and that the fall in systemic venous pressure precedes both these changes. These findings, which are contrary to those of Earle, Farber, Alexander, and Eichna (1949), suggest that the diuresis is due solely to increased tubular load. Reduction of the systemic venous pressure in congestive cardiac failure by venous occlusion of the thighs is not accompanied by a significant increase in renal plasma-flow or glomerular filtration. It follows that, although a fall in systemic venous pressure in such cases may increase cardiac output and may reduce renal venous pressure, these effects are incapable of measurably increasing renal plasma-flow or glomerular filtration. In the patient who had the highest systemic venous pressure, its reduction by venous occlusion of the thighs was accompanied by a transient but significant diminution in tubular reabsorption. It is therefore conceivable that a greatly elevated renal venous pressure may depress renal function by increasing tubular reabsorption. The results of the present investigation lead to the conclusion that the increase in renal plasma-flow, glomerular filtration rate, and urine flow which follows the intravenous administration of digoxin to subjects with congestive cardiac failure is due to augmentation of the cardiac output, which results from the direct action of digoxin upon the failing myocardium. The fall in systemic venous pressure which accompanies these changes is not responsible for the improvement observed in renal function, but merely reflects the more efficient emptying of the right ventricle. The limited nature of the studies reported here, which did not include observations concerning the excretion of electrolytes, precludes any deeper interpretation of the findings.

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Summary

1. The renal function in 12 cases of untreated and five cases of treated congestive cardiac failure of rheumatic, hypertensive, or ischaemic origin was studied by the urinary clearance of diodone and inulin.

2. In four of seven untreated patients with cardiac failure, intravenous digoxin produced an immediate fall in systemic venous pressure, which was followed by a rise in renal plasma-flow, glomerular filtration rate, and urine flow; the filtration fraction fell slightly in three cases, while tubular reabsorption decreased. In the remaining three patients the systemic venous pressure did not fall; in two the renal function was unaltered, and in one it was significantly depressed.

3. Reduction of systemic venous pressure by venous occlusion thigh cuffs in five patients with untreated cardiac failure produced no significant alteration in

the renal plasma-flow or glomerular filtration rate. In one subject there was a transient increase in the urine flow.

4. The significance of these findings is discussed.

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INFECTIVE HEPATITIS AND CIRRHOSIS OF THE LIVER[1]

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With Plates 32 to 37

The role played by infective hepatitis in the causation of cirrhosis of the liver has yet to be fully ascertained. Owing to the lack of a susceptible laboratory animal the problem cannot be settled by the experimental method. A solution is possible only by clinical and pathological studies from different parts of the world where the disease occurs against different backgrounds. For this reason a clinical study of a series of cases of infective hepatitis met with in Ceylon is here reported with special reference to the complications leading to cirrhosis.

Material

During a period of five years and 10 months between 1945 and 1950, 135 patients were admitted under our care at the General Hospital, Colombo, suffering from jaundice which was diagnosed as infective hepatitis or from its complications. Twenty-five cases ended fatally, and autopsies were available in 11. In addition seven patients were admitted for portal cirrhosis in whom a clear history was obtained that the disease was preceded by a severe attack of jaundice. In two of these seven cases it is possible that the disease was directly due to dietetic deficiency. These 142 cases form the subject of this paper. The age-, sex-, and racial distribution of cases was as follows:

Race	*Jaundice*	*Cirrhosis with history of jaundice*
Sinhalese . . .	112	7
Tamils . . .	10	..
Muslims . . .	7	..
Indians . . .	3	..
Burghers . . .	3	..
	135	

Age	*Jaundice*		*Cirrhosis*	
	Male	*Female*	*Male*	*Female*
Up to 9 years	4	1	..	..
10–19 „	19	8	..	..
20–29 „	33	16	..	1
30–39 „	18	8	2	..
40–49 „	11	4	1	..
50–59 „	6	2	2	..
60–69 „	3	1	1	..
Over 70 „	1	..	..	..
	95	40	6	1

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Cases admitted with jaundice

Onset

In 86 patients the onset was characterized by malaise, anorexia, and fever. They were generally in good health until they noticed a distaste for food, or even nausea; soon after this fever set in, and after an average period of four days the urine was found to be dark-coloured and the conjunctivae yellow. Twenty-five patients had only malaise and anorexia at the onset, without fever. These symptoms were followed by jaundice. The longest interval between the onset of gastric symptoms and the appearance of jaundice was eight days. In 24 cases jaundice was the first symptom noticed.

Clinical course

In respect of the subsequent clinical course the cases fall into four distinct categories.

1. *Simple jaundice.* In 107 patients the subsequent clinical course was that of simple jaundice. After the onset of jaundice the temperature in those who had fever came down to normal in three or four days; in one case the fever lasted over a week. The temperature was generally not high, and rarely exceeded 101° F. In 36 patients there was vomiting for several days. The gastric symptoms gradually settled down, appetite improved, and a week to 10 days after the appearance of jaundice the patients were generally well except for the jaundice and a feeling of malaise. Epigastric pain, as a rule of a dull nature, but more severe in a few cases, was experienced by 95 patients after the onset of symptoms, and the liver was enlarged, palpable, and tender in 74 patients on their admission. In five patients the lower border of the liver was palpable four finger-breadths or more below the costal margin, in 11 three finger-breadths, in 26 two finger-breadths, and in the rest one finger-breadth. The spleen was palpable in nine cases one or two finger-breadths below the costal margin. Neither bradycardia nor pruritus was a prominent symptom; only five patients complained of pruritus. Eleven had salivation. The stools were clay-coloured on admission in 13 cases; in the others they were of normal colour, though pale. Examination of the urine showed bile-pigment in 104 cases and in three this test was negative. These three patients had apparently been admitted in the recovery phase, for the van den Bergh reactions were indirect, and the average icterus index 17. Bile-salts were present in the urine of 63 patients, and absent in 40. They were always present with bile-pigment, never alone. Urobilin was detected in the urine of 93 patients, in an average dilution of one in ten. There was albumin, usually a trace, in the urine of 43 patients. The haematological findings and the results of liver function tests are given in Tables I and II. The subsequent duration of the illness varied widely. Twenty patients recovered from their jaundice within the comparatively short period of two weeks. Thirty-nine patients took between two and four weeks to recover, and 32 patients were ill for a period varying between one and two months. In 10 patients the illness was much prolonged, the average duration being 90 days, and two patients took nearly four months to recover. The clinical picture was

essentially similar irrespective of the duration of the jaundice, and when these patients were discharged from hospital the jaundice had cleared up, the urine was free of bile, and the liver had returned to normal size. Five patients were removed from hospital before recovery. Four of these were improving, but in one the jaundice was deepening and the icterus index, which was 80 on his admission, was 100 after 31 days in hospital, when he was removed. One patient died in hospital. This was a woman, aged 53 years, admitted with a history of jaundice of three months' duration. The onset was with anorexia, vomiting, and fever. There was no previous history of jaundice or abdominal colic. After a few days the vomiting and anorexia passed off, but the jaundice persisted. As she still had jaundice after three months, and the upper abdomen was swelling, she was admitted to hospital. On her admission the liver was enlarged to five finger-breadths below the costal margin. The spleen was not palpable, and the abdomen was soft. The temperature was 100° F. There was deep jaundice, and bile-pigment was present in the urine, but the stools were normal in colour. X-rays showed no calculi. Two months later the patient still had jaundice, and the liver was at the level of the umbilicus. At an exploratory laparotomy the liver was found uniformly enlarged, green in colour, and of firm consistence. There was no evidence of extrahepatic obstruction. Biopsy was done, and microscopic examination showed cellular infiltration consisting of round cells, mononuclear cells, and spindle-shaped cells in the larger interlobular spaces. There were also some fibrous strands, and the cells and fibres were extending into the smaller interlobular spaces, partially outlining the lobules. The cellular proliferation was also extending into the periphery of the lobule, and here and there two or three liver cells could be seen isolated and surrounded by fibrous tissue. Polymorphs were conspicuous by their absence. Inside the lobule the liver cells appeared healthy, there was no fat, and no disorganization of the liver cords. In some places bile was seen in cells around the central veins. The picture was that of early biliary cirrhosis (Plate 32, Fig. 1).

2. *Fulminant cases.* In 10 cases the disease ran a fulminant course. The onset was as in simple jaundice. There was anorexia, nausea, and pain over the liver. In three patients there was also fever. In a few days jaundice appeared, but the gastric symptoms did not abate with the appearance of jaundice; in three patients they increased, and there was vomiting as well. In about a week from the onset nervous symptoms set in, consisting of disorientation, excitement, delirium, drowsiness, or lethargy, all finally progressing to coma, and the patients died within the next two or three days. In eight cases the duration of the illness was altogether less than 10 days. The following is a typical history.

A woman of 24 years developed fever and anorexia of rapid onset. Three days later she also had jaundice and vomiting; after two days she became unconscious, and was admitted to hospital. On examination she was deeply jaundiced and comatose; the corneal reflexes were absent, and the plantar reflexes extensor. The liver and spleen were not palpable. She was treated with intravenous glucose and methionine, but died in 24 hours.

In two cases the illness was more prolonged, and death took place on the

14th and 20th day respectively. Post-mortem examinations were made in two cases: in one the patient had died on the 20th day, and in the other death had occurred within 10 days of the onset. In both the liver was smaller than normal, and had a mottled 'nutmeg' appearance on the surface. The normal shape and consistence were retained. The cut surface showed minute reddish and yellowish areas diffusely scattered (Plate 32, Fig. 2*a*). There was bleeding into the stomach in one case, and into the lungs in the other. There were no oesophageal varices. There was no free fluid in the abdomen. Microscopically the lobular architecture was preserved and the reticulin framework could be made out, but the liver cells had almost disappeared except a few cells in the periphery of the lobule. Bile-ducts were prominent in the portal tracts, and outlined the lobules like a 'stockade' (Plate 32, Fig. 2*b*). In the case in which life was prolonged to 20 days there was a cellular appearance in the lobule due to proliferation of the sinusoidal cells. There was endophlebitis of the central vein in some areas.

3. *Acute massive necrosis.* There were nine cases which also ended fatally, but in which the clinical course was significantly different. The onset was similar to that in the cases already reported. An attack of anorexia, nausea, and pain in the epigastrium was followed by jaundice within a few days. Three patients had fever during the early stages. A few days after the appearance of jaundice the gastro-intestinal symptoms cleared up, and the patients were apparently getting on well, when suddenly the condition took a turn for the worse. The average duration of this satisfactory interval was 20 days, but it was as short as 12 days in one and as long as 34 days in another patient. The deterioration was in most cases characterized by a return of the gastric symptoms; this was soon followed by the appearance of the nervous symptoms described above, and the subsequent course was similar to that observed in the fulminant group; all the patients died within an average period of 38 hours, the extremes being nine hours in one case and 84 hours in another. Two patients developed ascites towards the end; one vomited blood. Post-mortem examination was done in six cases. The livers were greatly contracted and soft, and the capsules markedly wrinkled. Section showed extensive yellowish-green areas with intervening areas of reddish tissue (Plate 33, Fig. 3*a*). The naked-eye appearances were quite different from those seen in the livers of fulminant cases. Microscopically there were extensive areas of necrosis, in which no lobular structure could be made out and the reticulin framework, but no liver cells, could be seen; bile-ducts were prominent (Plate 33, Fig. 3*b*). In some areas in the midst of this reticular tissue a few surviving liver cells could be made out, but it was difficult to determine their position in the lobule (Plate 33, Fig. 3*c*). In one specimen there were small areas in which the lobular architecture was maintained, but there was centrilobular necrosis and cellular infiltration in the portal tracts (Plate 34, Fig. 3*d*). The following is an illustrative case.

A man of 21 years developed anorexia and upper abdominal pain; a few days later jaundice set in. After the appearance of jaundice the gastro-intestinal symptoms improved. Jaundice persisted, though he was otherwise well, and on the 28th day of illness he was admitted to hospital because of continued

jaundice. On examination the patient was deeply jaundiced, the serum-bilirubin was 8 mg. per 100 ml., the van den Bergh reaction was biphasic, and there was bile in the urine. Six days after admission the patient became drowsy and disorientated, and soon went into coma. He died within 24 hours of the commencement of nervous symptoms. At post-mortem the condition was that of massive necrosis, as described above.

4. *Subacute massive necrosis.* In eight patients the onset and course of the illness in the early stages were similar to those found in the case of patients who died of acute massive necrosis. But after a variable period of jaundice which was about 37 days on the average, the extremes being 14 days and 80 days, it was found that free fluid was collecting in the abdomen. The appearance of ascites was followed by oedema of the legs in six patients. Their general condition, which was good up to this time, was also found to have deteriorated; the appetite failed, malaise and general weakness increased, and some patients were mentally dull. Diminution in the quantity of urine passed was a prominent symptom in four patients. Two patients had bleeding from the gums, one bled from the rectum, and one had haematemesis. The subsequent course of the illness was characterized as a rule by periods of improvement and deterioration. Two patients were discharged apparently cured after 150 and 180 days respectively. The jaundice had cleared up, ascites had disappeared, and the urine was free of bile when they left the hospital. One patient had oliguria, and subsequently coma, after paracentesis, and was taken home. Five patients died in coma after an average period of 77 days of illness. Persistent oliguria was an important symptom towards the end. Post-mortem examination was done in three cases. The liver was found contracted and atrophic. On the surface large yellowish nodules alternated with depressed reddish areas in two cases (Plate 34, Fig. 4*a*) while in one the nodules were smaller and approximated to the condition found in toxic cirrhosis. Microscopically there were extensive areas in which no liver cells were seen but only condensed reticulin, and in which proliferating bile-ducts were conspicuous. Side by side with these were hyperplastic nodules of liver tissue without the normal lobular architecture (Plate 34, 4*b*). Elsewhere there were groups of normal lobules. The following case-histories illustrate the clinical course of the cases that ended in death and of those that ended in recovery.

1. A man aged 40 years was admitted on September 24, 1949, with jaundice of three months' and oedema of the legs of about 10 days' duration. The onset was accompanied by anorexia, nausea, slight fever, and headache. His diet prior to jaundice consisted of rice and vegetables daily and meat twice a week. After jaundice began he had been able to eat very little of his normal meals. On examination he was jaundiced; the van den Bergh reaction was biphasic, the serum-bilirubin 2 mg. per 100 ml. and the Takata–Ara and cephalin-cholesterol tests strongly positive. The plasma-albumin was 4·31 gm., globulin 3·4 gm., cholesterol 200 mg. per 100 ml., and alkaline phosphatase eight Bodansky units. The red cells were 3,730,000 per c.mm., white cells 4,600 (polymorphs 63 per cent., lymphocytes 37 per cent.), and platelets 156,000. The Kahn and cardio-lipin tests were negative; the urine contained bile-pigment and albumin, but no bile-salts. The stools contained stercobilin, but no amoebae

or helminthic ova. There was ascites and oedema of the legs. He was given a high protein diet consisting of fish, meat, malted milk, rice, and vegetables; glucose was given freely in his drinks, and methionine 1,500 mg. and calcium lactate daily by mouth. Ten days later ascites was still present, and he was given in addition 50 ml. of 25 per cent. glucose solution and calcium gluconate 10 ml. intravenously each day. Ten days later he developed oliguria and bleeding from the gums. He was then given methionine 1 gm. intravenously each day in addition to the above treatment. During the next week his condition was grave; there was bleeding from the rectum, ascites was increasing, and he was getting drowsy. On 21.10.49, 160 ounces of yellowish fluid were removed from the abdomen by paracentesis. On 24.10.49 the patient was conscious, the urine had increased, and the general condition was improved. He remained better, but ascites gradually increased; paracentesis was repeated on 1.11.49, and 148 ounces of fluid were removed. It was repeated again on 9.11.49, when 200 ounces were removed. The van den Bergh reaction was now indirect; there was no bile in the urine, but the plasma-proteins were albumin 1·78 gm., globulin 3·00 gm., and fibrinogen 0·22 gm. per 100 ml.; the Takata–Ara and cephalin-cholesterol tests were strongly positive. On 10.11.49 the patient had diarrhoea, and became drowsy and disorientated; he died four days later in coma. Post-mortem examination showed a nodular contracted liver, weighing 28 ounces; its microscopic appearance was as described above.

2. A boy aged 13 years was admitted on April 21, 1948; he had had jaundice for one month and swelling of the abdomen and legs for two weeks. The jaundice had come on insidiously, without symptoms. There was no history of injections, or of contact with cases of jaundice. His diet consisted of rice and vegetables, with fresh or dried fish three times a week. On examination there was ascites, oedema of the legs, and jaundice. The liver and spleen were not palpable. The van den Bergh reaction was biphasic, the serum-bilirubin 9 mg. per 100 ml., and the plasma-proteins 6·33 gm. per 100 ml. (albumin 4·28, globulin 1·76, fibrinogen 0·29 gm.). The Takata–Ara reaction was positive. The red blood-cells were 2,700,000 per c.mm., the haemoglobin 45 per cent., white cells 8·800 per c.mm. (polymorphs 55 per cent., lymphocytes 43 per cent., eosinophils 2 per cent.), and reticulocytes 1 per cent. The urine showed bile-pigment and urobilin in a dilution of 1 in 20, but contained no bile-salts. The patient was given a high protein diet, malted milk, and glucose in drinks, with the addition of 50 ml. of a 25 per cent. solution of glucose intravenously each day. The jaundice gradually cleared, and on 25.5.48 the urine contained no bile-pigment, but the ascites had increased. Paracentesis was done and 120 ounces of fluid were removed; the abdomen refilled gradually, and a month later 116 ounces were removed. On 17.7.48 treatment with ammonium chloride, dehydrocholin tablets, and periodical injections of mersalyl, was begun. The abdomen did not fill up rapidly, but the ascites continued. On 12.8.48 daily intravenous injections of protein hydrolysates (amigen, casydrol) were started. By 31.8.48 the ascites was much reduced. The Takata–Ara reaction was weakly positive, and the plasma-proteins 6·91 gm. per 100 ml. On 30.9.48 there was no ascites, the patient's general condition was good, and he was taking food well; the red blood-cells were 3,600,000 per c.mm., and the haemoglobin 65 per cent. He was discharged, and has since remained in good health.

Cases admitted with Cirrhosis of the Liver

During this period seven patients were admitted under our care for cirrhosis with a clear history of a severe attack of jaundice preceding the ascites. They

were all admitted on account of ascites, which had existed for an average period of five months. Four patients also had oedema of the legs, which had set in later than the ascites. The liver was not palpable in any patient, but the spleen was palpable in three; in one it reached the umbilicus, and in two it was felt two and three finger-breadths below the costal margin respectively. The history of onset in five patients was similar to that of infective hepatitis. They had been in good health until anorexia, malaise, and nausea set in, followed by jaundice. The diet prior to the attack had been good. In these five patients the intervals between the attack and the onset of ascites were three months, three months, five months, eight months, and one year respectively. In two patients the history was different. One, a man of 46 years, had developed a state of chronic ill health with loss of appetite. His diet during this period was rice conjee or kurakkan in the morning and rice, with one vegetable curry, for the noon and night meals. He ate meat or dried fish only two or three times a month. His appetite was poor, and the quantity consumed at each meal was little. He often went to bed without his night meal. At the end of seven months he developed jaundice, which was followed later by ascites. The jaundice gradually cleared up, but the ascites persisted. The other, a man of 55 years, had a diet of yams for lunch and rice with vegetables for dinner for one year, with no milk, eggs, meat, or fish. He then developed jaundice, which lasted for six months and cleared up. Three years later ascites gradually appeared, and had lasted for 18 months when he entered hospital. The subsequent clinical course of these seven patients was as follows. The last-mentioned patient, who had ascites for 18 months, became drowsy and died in coma a week after his admission. Post-mortem examination showed the condition of nodular hyperplasia (toxic cirrhosis of Mallory) (Plate 35, Fig. 5*a*). The liver was contracted and coarsely nodular. Microscopically the reticular framework had condensed into scar tissue, and the surviving liver cells had proliferated into hyperplastic nodules without the normal lobular architecture, while surviving liver lobules had recovered and hypertrophied (Plates 35, 36, Figs. 5*b*, 5*c*, 5*d*). The one female patient, aged 28 years, was under medical treatment for over five months before she was transferred to a surgical ward. During this period paracentesis was done on seven occasions, and she had three severe haematemeses. She died after an operation for spleno-renal anastomosis. Biopsy showed hyperplastic nodules with dense strands of fibrous tissue irregularly scattered throughout the liver. One patient left hospital after 30 days of treatment with no improvement. Four patients recovered, and were free of ascites and in good health when they left the hospital; one patient was in hospital for 44 days, and the other three for about two months. The following is an illustrative case.

A man of 65 years was admitted on April 22, 1948; he had had swelling of the abdomen and feet for two months. Three months earlier he had developed jaundice, for which he was given ayurvedic treatment. His diet before his illness was good; in addition to rice and vegetables he had meat and fish daily, and took milk in his tea. He also took alcohol daily. After the onset of jaundice his diet was poor, consisting of rice with vegetables, but no meat, fish, or milk. He also gave up alcohol. After three months he had severe vomiting for several

days, and felt very weak. When he recovered from this attack he noticed that he had ascites. On examination there was ascites and oedema of the legs; the liver and spleen were not palpable. There was no jaundice; the van den Bergh reaction was indirect, and the serum-bilirubin 0·2 mg. per 100 ml. The urine contained no bile-pigment, bile-salts, or albumin, but urobilin was detected in a dilution of 1 in 20. The Takata–Ara reaction was positive, and the plasma-proteins were 4·79 gm. per 100 ml. (albumin 2·58 gm., globulin 1·92 gm., fibrinogen 0·29 gm.). The haemoglobin was 45 per cent., red cells 2,600,000 per c.mm., and white cells 3,200 per c.mm. (polymorphs 67 per cent., lymphocytes 33 per cent.). He was given a high protein diet containing liver, meat, fish, eggs, and vitamin B complex. His ascites did not improve, and from 4.5.48 treatment with an ammonium chloride mixture, with intravenous mersalyl and dehydrocholin, was given at intervals of four or five days. The urine output increased, and the ascites and oedema diminished slightly. The plasma-proteins at this stage were albumin 4·46 gm., globulin 1·42 gm., and fibrinogen 0·11 gm. per 100 ml. By the end of the month the ascites and oedema were much less. The liver was not palpable. He was discharged on 21.6.48 free of ascites and oedema.

Laboratory Findings

The haematological findings on admission in the subjects examined are given in Table I. There was great variation in the haemoglobin percentage and red-cell counts. Severely anaemic patients were found both among the mild cases and among those with serious complications. But the incidence of serious complications among the anaemic patients was double that found among those who were not anaemic. Of 58 patients whose haemoglobin was below 70 per cent., 22·4 per cent. had fatal complications, compared with 10·6 per cent. of the 66 patients who had higher haemoglobin figures. There was no significant variation in the platelet counts; the figures found even in fatal cases were within normal limits. There was a leucopenia in 15·6 per cent. of cases, 42·2 per cent. had normal counts, and 42·2 per cent. a leucocytosis. The leucocytosis was polymorphonuclear. While leucopenia was found among the cases of simple jaundice, leucocytosis was almost the rule in patients with massive necrosis of the liver; three-fourths of these patients had leucocyte counts of over 10,000 per c.mm.

Liver function tests. Table II gives the results of certain liver function tests carried out as a routine, and their relationship to simple and fatal cases. The van den Bergh, icterus index, Takata–Ara, and alkaline phosphatase tests were carried out according to the methods described by Gradwohl (1938). The cephalin-cholesterol test was carried out as described by Hanger (1939); cholesterol esters were determined by the method of Bloor and Knudson (1916), and plasma proteins according to the method described by Beaumont and Dodds (1939). It was found that the mortality rate of the more severely jaundiced patients was much greater than that of those with less jaundice, irrespective of the nature of the van den Bergh reaction. The mortality in patients with a serum-bilirubin higher than 5 mg. per 100 ml. was 31·1 per cent.; with lower values it was 8·7 per cent. There were no deaths among patients with an indirect van den Bergh reaction. In every case examined the direct van den

TABLE I. *Haematological Findings*

Haemoglobin			Red cells			White cells: Total			White cells: Polymorphs			White cells: Lymphocytes			Platelets		
per cent. (Dare's)	Number of cases (124)	Deaths	Millions per c.mm.	Number of cases (123)	Deaths	Thousands per c.mm.	Number of cases (128)	Deaths	Thousands per c.mm.	Number of cases (126)	Deaths	Thousands per c.mm.	Number of cases (126)	Deaths	Thousands per c.mm.	Number of cases (124)	Deaths
< 50	10	2	1–2	1	0	< 5	20	1	< 3	6	1	< 3	93	14	100	4	3
51–60	19	4	2–3	12	4	5–10	54	5	3–6	94	13	> 3	33	6	100–200	64	11
61–70	29	7	3–4	48	11	> 10	54	15	> 6	26	6	..	..	..	200–300	55	7
71–80	44	3	4–5	56	5	..	..	..	..	..	..	..	..	..	> 300	1	0
81–90	19	4	> 5	6	0												
91–100	3	0															

TABLE II. *Liver Function Tests*

Icterus index	Number of cases (126)	Deaths	Van den Bergh reaction	Number of cases (125)	Deaths	Plasma alkaline phosphatase (Bodansky units)	Number of cases (80)	Deaths	Cephalin-cholesterol test	Number of cases (92)	Deaths	Takata-Ara reaction	Number of cases (123)	Deaths	Blood-cholesterol (mg./100 ml.)	Number of cases (90)	Deaths	Cholesterol esters (%)	Number of cases (30)	Deaths	Plasma-proteins (gm./100 ml.)	Number of cases (114)	Deaths	Ascites
			Qualitative:																		Albumin:			
5–25	29	0	Immediate direct	5	2	< 10	28	4	Negative	23	1	Negative	50	2	100–150	10	0	20–30	2	1	0–2·5	11	5	4
26–50	65	14				10–20	44	9	Weak	2	1	Weak	5	0	151–200	43	10	31–40	11	3	2·6–3·5	56	8	2
51–75	12	1	Biphasic direct	101	22	> 20	8	1	Positive	38	6	Positive	51	11	201–250	23	1	41–50	13	4	3·6–4·5	39	4	3
76–100	18	8							Strongly positive	29	7	Strongly positive	17	10	> 250	14	4	51–60	4	0	> 4·5	8	8	0
> 100	2	1	Indirect	19	0																Globulin:			
			Quantitative: (mg./100 ml.)																		0–1·5	3	2	0
			< 2	36	0																1·6–2·5	66	11	5
			2–5	44	7																2·6–3·5	39	5	2
			5·1–7·5	20	8																> 3·5	6	2	2
			7·6–10	12	5																			
			> 10	13	1																			

Bergh reaction became indirect before it finally became negative. The alkaline phosphatase test, which estimates the excretory function of the liver, gave similar results; a greater degree of obstruction went with a higher fatality. The estimation of plasma-proteins was found to be of value in determining the extent of the liver damage, and in judging whether patients were improving. Patients in whom the plasma-albumin was low on admission had a worse prognosis than those in whom it was normal. There were no deaths among subjects who had 4·5 gm. or more of plasma-albumin per 100 ml. With values between 3·6 gm. and 4·5 gm. the mortality was 10·25 per cent., between 2·6 gm. and 3·5 gm. 14·28 per cent., and below 2·6 gm. 45·54 per cent. Thus the mortality rate steadily increased as the plasma-albumin decreased. In the individual case periodic estimation of the plasma-albumin gave valuable information as to whether the patient was improving or not. The prognosis was worse when the plasma-globulin was either too high or too low than when it was within the normal range. In 105 cases in which the globulin was between 1·6 gm. and 3·5 gm. per 100 ml. the mortality was 15·2 per cent., as against 44·0 per cent. mortality in the nine cases in which it was above or below that range. The Takata–Ara and cephalin-cholesterol tests are empirical procedures which show whether hepato-cellular degeneration is present. The cephalin-cholesterol test was positive in 67 out of 92 cases examined (72·8 per cent.), and the incidence of fatal cases among them was 19·4 per cent. Among the 25 cases with negative and doubtful positive results the mortality was 8 per cent. The Takata–Ara test was positive in 68 out of 123 cases (55·2 per cent.), and the mortality among these patients was 30·8 per cent. Thus the cephalin-cholesterol test is the more sensitive, and is positive with a less severe degree of degeneration. A positive Takata–Ara reaction indicates more serious damage; this test was positive in nearly every case of acute and subacute necrosis or of cirrhosis of the liver.

Aetiology

The following points from the previous history of our patients are of interest.

1. *Contacts and multiple infections.* In three cases there was a history of contact and of multiple infections in the family. One woman attended her three-year-old child, who had jaundice for nearly two months. At the end of this period she herself developed jaundice, and died three weeks later of acute massive necrosis of the liver. One patient gave the history that her elder sister had had jaundice for several weeks, and had recovered; then her younger sister, and a week later the patient herself, got jaundice. The wife of a third patient had jaundice for about a month. Two weeks later, after she recovered, he himself became jaundiced.

2. *Parenteral injections.* Nine patients with simple jaundice had had intravenous neoarsphenamine injections at venereal disease clinics before they had jaundice. The intervals between the last injection of the series, which usually consisted of eight weekly injections, and the appearance of jaundice were 21, 28, 39, 45, 60, 70, 85, 90, and 120 days respectively. Four patients belonging to the groups with acute and subacute massive necrosis gave a similar history of

injections. The intervals in their cases were 14, 60, 60, and 80 days; all these four patients died. One patient had received anti-rabies inoculation 90 days prior to the jaundice; another was attending a diabetic clinic for insulin injections daily for several months. The clinical histories of these two patients differed in no important respect from those of the patients who had a history of parenteral injections.

3. *Diet.* The importance of diet in the aetiology and prognosis of liver diseases is being increasingly recognized. A dietetic history was available in 97 cases. The diets have been classified under the following headings, as described

TABLE III

Categories of Diet in relation to Clinical Varieties and Deaths

	Diet A		*Diet B*		*Diet C*		*Diet D*	
	Cases	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*	*Cases*	*Deaths*
Simple jaundice	67	1	9	0	2	0	2	0
Fulminant jaundice	1	1	..	..	1	1	..	..
Acute massive necrosis	1	1	2	2	..	..	..	..
Subacute massive necrosis	2	1	2	1	1	1	..	..
Toxic cirrhosis	2	1	2	1	1	0	2	1
	73	5	15	4	5	2	4	1
Percentage of deaths		6·84		26·6		33·3		
Percentage of complications		8·2		40		55·5		

by Fernando, Medonza, and Rajasuriya (1948). Diet A was one in which, besides the staple food (rice or preparations made of flour), vegetables and some animal food such as dried fish, fresh fish, or meat were consumed daily. Generally two good meals were taken, at noon and at night, and a light meal in the morning. Diet B was similar except that the animal foods were taken only about twice a week; the number of meals each day was the same as in diet A. Diet C was similar to diet B except that no animal proteins were taken. Diet D was very poor, and normally consisted of rice or preparations of flour, or some yams, with one vegetable. Meat or fish was taken only about once or twice a month, or not at all; moreover, the quantities taken at each meal were insufficient, and sometimes there was only one meal a day. In all these diets the amount of milk and eggs consumed was negligible. Table III gives the categories of diet in relation to the different clinical groups of patients. It will be seen that the serious complications of a fulminant course and massive necrosis increased in frequency as the diets became more and more deficient in animal proteins.

4. *Alcohol.* A history of alcoholism was obtained in nine patients, of whom six had simple jaundice; the average duration of jaundice in these patients was 24 days. Two patients in the group of toxic cirrhosis, and one in that of subacute massive necrosis, were alcoholics; two of these patients died in hospital, and one left hospital unrelieved.

Discussion

The history of onset and the early clinical symptoms were similar in all these cases of jaundice, irrespective of a history of parenteral injections. All the cases occurred in subjects who had been well at the time of onset of the illness. Its subsequent course was not the same in all. In 10 patients the illness took a fulminant course, and most of these died within 10 days. In two cases autopsy showed that the reticular framework of the lobule was preserved, while the liver cells had almost disappeared except for a few cells at the periphery. These appearances were the same as those recorded in similar cases elsewhere (Lucké, 1944*a*). The remaining cases fall into two categories. The first contains the great majority of patients (107); in these the disease ran a simple course, in which jaundice was the main disability, and the jaundice ultimately cleared up completely in all who were long enough under observation, with one exception to which reference will be made later. Biopsy studies in non-fatal cases of infective hepatitis have shown that the essential pathological feature is an acidophil degeneration or necrosis of liver cells, most marked around the central veins, and an inflammatory reaction particularly in the portal regions. With recovery from the illness complete restitution of the liver lobule takes place and the inflammatory reaction disappears (Dible, McMichael, and Sherlock, 1943; Lucké, 1944*b*; Mallory, 1947). Figs. 6*a* and 6*b* (Plate 37) are taken from a biopsy section from one of our patients on the 20th day of jaundice, showing the healing stage. In the second category the onset and early symptoms were indistinguishable from those of simple jaundice. The patients, like those in the first category, had progressed well for some weeks when an unexpected turn for the worse occurred. In some cases symptoms of liver failure rapidly supervened, and the patients died within two or three days. In some the symptoms were not so serious, the patients survived, and ascites became a prominent symptom. The subsequent course of the illness was characterized by periods of improvement and periods of deterioration, until ultimately the patients died of liver failure, haemorrhage, or intercurrent infection, or recovered after a protracted illness. The macroscopic and microscopic appearances of the liver at autopsy were quite distinct from those seen in the fulminant cases. In the latter the normal shape and consistence of the liver were retained, while the surface had a mottled appearance; but in the acute cases of this second category the livers were greatly contracted and soft, and the capsule wrinkled. Section showed large yellowish-green areas, with intervening areas of reddish tissue. Microscopically there were extensive areas in which no lobular structure or liver cells could be made out, but only reticulin, connective tissue, blood-vessels, and bile-ducts. There were occasional groups of surviving liver cells which had no definable location within a lobule. Rarely liver lobules of normal architecture, but with centrilobular necrosis, were seen. In patients who had developed ascites the livers were nodular, and sections showed extensive areas of condensed reticulin which were rendered conspicuous by proliferating bile-ducts, alternating with areas in which there were masses

of liver cells without the normal lobular structure, or groups of hypertrophied normal lobules.

Two views exist as to the relationship of infective hepatitis to acute and subacute massive necrosis. One view is that idiopathic massive necrosis represents the end stage of fatal epidemic hepatitis (Lucké, 1944*a*); the other view is that it is a complication supervening on infective hepatitis in subjects whose livers are already weakened and unable to bear the further strain caused by this infection (Cockayne, 1912). Himsworth and Glynn (1944*b*), who produced in the experimental animal all degrees of massive necrosis purely by dietetic protein restriction, strongly supported the latter view. They pointed out the similarity of the clinical and pathological picture presented by infective hepatitis to that found in poisoning by toxic substances such as carbon tetrachloride and chloroform. The toxic effects are produced within a few hours, the lesion is a diffuse zonal necrosis, and if early death does not occur recovery follows with full restoration of the lobular structure. Acute and subacute massive necrosis, like dietetic massive necrosis, occur after a long latent period, during which the subjects are well; a rapid deterioration of health occurs. The liver shows extensive areas of necrosis, with areas of surviving lobules. The lesion is not diffuse but regional. Our findings, summarized above, support the view that yellow atrophy is a complication, not the natural end stage, of fatal infective hepatitis. What determines this complication? In dietetic massive necrosis the sole factor is the composition of the blood reaching the liver. A deficiency of protective aminoacids such as methionine induces necrosis, while an adequate content prevents it. With less deficient diets, which produce only partial massive necrosis, the left lobes are more constantly affected because they receive a smaller supply of protective factors, in the blood draining the colon, than that given to the right lobe by blood from the small intestine. Similarly areas subject to pressure by neighbouring organs, and therefore with a comparatively deficient blood-supply, are more liable to necrosis than areas in which the circulation is free. Himsworth and Glynn (1944*a*) suggested that the same mechanisms operate in the production of massive necrosis complicating infective hepatitis. Swelling of the liver inside the rigid capsule may restrict the circulation of blood to certain areas. This may be sufficient by itself to determine a state of deficiency in those areas, irrespective of the presence of adequate protective factors in the blood, but when there is a deficiency of protective aminoacids in the blood vascular factors may operate more easily. The higher mortality rates of infective hepatitis and serum jaundice in subjects who have had deficient diets, compared with those who have been well fed, in spite of the operation of the same vascular factors, supports this view. The over-all mortality in the Central Mediterranean Forces from infective hepatitis and serum jaundice was estimated at 0·2 per cent., while the rates in Brazilian natives and in Africans were 2·4 per cent. and 3 per cent. respectively. The higher incidence has in each instance been correlated with dietary deficiency (Stokes and Miller, 1947). The findings in our cases support the above suggestions as to the mechanisms producing massive necrosis. It will be observed from

Tables I, II, and III that a higher proportion of fatal complications occurred in patients who were anaemic, whose jaundice was very severe, whose plasma-proteins were low, and whose diet was deficient in proteins. Jaundice in infective hepatitis has been attributed to obstruction of the intercellular canaliculi and to cellular inadequacy (Dible, McMichael, and Sherlock, 1943). The van den Bergh reaction helps to distinguish between jaundice due to pure obstruction and that due to cellular damage, the former giving the immediate reaction and the latter the biphasic (McNee, 1923). But in our series the percentage of deaths in patients with the immediate reaction was double that found in subjects with the biphasic reaction. Features common to most fatal cases were a high serum-bilirubin content and a high icterus index. The higher incidence of fatal complications in subjects with severe jaundice, irrespective of the qualitative nature of the van den Bergh reaction, serves to emphasize the importance of obstruction to free circulation inside the lobule. Obstruction, besides causing high bile-retention, must also interfere with the circulation of blood. Ninety-five patients in the group of simple jaundice had epigastric pain, and in 74 the liver was enlarged, palpable, and tender on admission. This shows that considerable swelling of the liver is a feature of infective hepatitis.

Anaemia is not a prominent symptom of infective hepatitis and serum jaundice, and begins to appear only when complications such as haemorrhage set in. 'Profound anaemia is no more common in hepatitis after yellow-fever inoculation than it is in infective hepatitis' (Findlay, Martin, and Mitchell, 1944). The anaemia which was found in both mild and serious cases in our series may therefore be taken to represent the condition of the blood of the patients at the onset of the illness, and not the effect of the infection. Anaemia did not make dogs more susceptible than normal dogs to chloroform poisoning (Daft, Robscheit-Robbins, and Whipple, 1936). Since malnutrition is an important cause of anaemia in Ceylon (Nicholls, 1936), the greater frequency of fatal complications among the anaemic patients reflects not so much the influence of anaemia as that of malnutrition on the prognosis of infective hepatitis. This view is supported by the greater frequency of such complications in patients whose diet was deficient in protein, compared with those who had good diets. The percentage of severe cases with protein-deficient diets (diets C and D) was five times that which occurred with diets containing a daily ration of animal proteins. The plasma-proteins, and albumin in particular, depend on two factors, the functional efficiency of the liver and the protein content of the food. How much each factor contributed to the lowering of plasma-proteins in our patients could not be determined, but in view of the low protein content of the diet of most of the patients who had hypoproteinaemia, dietetic deficiency must have played an important part. Protein deficiency has been found to increase the susceptibility of the liver to the diffuse zonal lesions caused by hepatotoxic substances (Miller and Whipple, 1940; Messinger and Hawkins, 1940), as well as to the massive type of necrosis induced by such substances as trinitrotoluene (Himsworth and Glynn, 1939–42), in addition to the tendency of dietary deficiency alone to produce massive necrosis. The

fulminant course in some of our patients may have been related to their diet, but owing to their serious condition a dietetic history was available in only two cases, so that this point cannot be decided. In the massive type of necrosis sufficient histories were available to show the influence of diet.

While patients in whom the greater part of the liver is destroyed die with the clinical features of acute massive necrosis, those in whom sufficient tissue survives come to present the picture of subacute massive necrosis. Ascites, which is a prominent symptom of this condition, is largely caused by the diminution of plasma-proteins, but vascular obstruction alone may be sufficient. Of five patients examined, the total plasma-proteins and albumin were normal in one but greatly diminished in four, the average figures being 5·19 gm. and 2·86 gm. per 100 ml. respectively. In favourable cases the jaundice and ascites disappear gradually, and the patient becomes well. In others the jaundice disappears, but not the ascites, which may even increase. Ultimately the picture of portal cirrhosis is found. In a patient seen in this condition for the first time the absolute differentiation from Laennec's cirrhosis is hardly possible except by biopsy. The history of a severe attack of jaundice preceding the cirrhosis may help in the clinical differentiation. All gradations of the development of nodular hyperplasia (Mallory's toxic cirrhosis) from infective hepatitis through massive necrosis were represented in our material. However, infective hepatitis is probably not an essential precursor of massive necrosis. In two of our patients it appeared as if subacute massive necrosis, like the experimental dietetic massive necrosis, had occurred as a result of dietetic restriction alone. The subjects had for several months been having a diet grossly deficient in proteins, when suddenly they developed a severe and prolonged attack of jaundice, after which they developed portal cirrhosis. We have referred elsewhere to six cases in which a similar dietetic history was given (Fernando, Medonza, and Rajasuriya, 1948).

We have mentioned one case in the group of simple jaundice which differed from the others in its clinical course. In this patient jaundice persisted, and the liver steadily increased in size until, five months after onset, it reached the umbilicus. Exploratory laparotomy and biopsy showed a greatly enlarged, bile-stained, firm liver with the histological features of early biliary cirrhosis. The appearances were very similar to those of the variety of biliary cirrhosis following infective hepatitis described by Watson and Hoffbauer (1946) and attributed by them to persistent leakage of bile into the tissue-spaces around the cholangioles. The wall of the cholangiole seems to have so altered in permeability as a result of the infection as to allow bile to escape, as albumin escapes from the glomerulus in Type 2 nephritis (Ellis, 1942). Infective hepatitis would therefore seem to cause a form of portal cirrhosis characterized by persistent jaundice, great enlargement of the liver, and the absence of ascites. These are the classic features of biliary cirrhosis (Rolleston and McNee, 1929).

Whether diffuse fibrosis of the type found in Laennec's cirrhosis originates in infective hepatitis is very doubtful. It has been produced experimentally by two distinct procedures, the repeated administration at short intervals of a

hepatotoxic substance (Cameron and Karunaratne, 1936), and the production of prolonged fatty infiltration by a number of methods (Rich and Hamilton, 1940; Chaikoff, Connor, and Biskind, 1938; Chaikoff, Eichorn, Connor, and Entenman, 1943; Spellberg and Keeton, 1940; Himsworth and Glynn, 1944*b*). The essential requirement seems to be necrosis of liver cells and absorption of their autolytic products into the portal regions, inducing a fibrocytic reaction. Although second attacks of infective hepatitis occur, they are uncommon, and it is very unlikely that they will recur at the short intervals and over the long periods necessary to such a process. In all cases in our experience in which there was the history of a severe attack of jaundice preceding the onset of what appeared to be Laennec's cirrhosis, biopsy or autopsy, when available, has shown the toxic type, not Laennec's type, of cirrhosis (Fernando, Medonza, and Rajasuriya, 1948). A history of jaundice was sometimes available in genuine cases of Laennec's cirrhosis, but it was always of a mild attack, and was often associated with bouts of alcoholism or unusual periods of starvation. In cases in which there was an opportunity of examination at this stage, the liver was always found enlarged. The jaundice and enlargement rapidly disappeared with the discontinuance of alcohol and the ingestion of a good diet. Apparently the jaundice was due to obstruction caused by rapid accumulation of fat in the liver.

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Summary and Conclusions

1. A clinical study has been made of 140 patients admitted to hospital with infective hepatitis or its sequelae. Autopsy and biopsy material, where available, has been studied.

2. The majority of patients (76·4 per cent.) exhibited the clinical picture of simple jaundice; 7·1 per cent. had fulminant hepatitis and in most cases died within 10 days; 15·7 per cent. developed the complication of massive necrosis after a latent period during which they were apparently recovering. All varieties of this complication—acute massive necrosis, subacute massive necrosis, and nodular hyperplasia (toxic cirrhosis of Mallory) were represented. One patient developed biliary cirrhosis.

3. The natural sequel of infective hepatitis is either death from fulminant disease or recovery. The essential lesion is a diffuse zonal necrosis. In patients who recover the surviving liver cells of the lobule regenerate, and its complete,

restitution occurs. The cholangiole takes longer to recover; rarely it may be so altered in permeability as to allow bile to leak out. If this persists long enough the condition of biliary cirrhosis may develop. Massive necrosis, which is a different lesion and regional in distribution, is a complication, and seems to be determined largely by the nutritional state of the patient before and after the development of infective hepatitis.

4. Dietetic deficiency alone may be sufficient to cause massive necrosis in human beings. The history of two patients admitted with toxic cirrhosis suggested that the condition was of purely dietetic origin, and not a complication of infective hepatitis.

5. It is doubtful whether diffuse fibrosis of the type met with in Laennec's cirrhosis occurs as a sequel of infective hepatitis. The clinical picture in the late stages of nodular hyperplasia (Mallory's toxic cirrhosis) is, however, very similar to that seen in Laennec's cirrhosis, and is characterized by portal obstruction. In the clinical differentiation between the two conditions the history of a severe attack of jaundice preceding the cirrhosis is in favour of a diagnosis of toxic cirrhosis.

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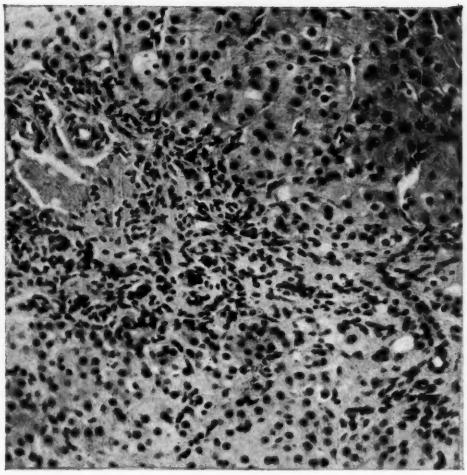

FIG. 1. Cellular proliferation in the portal tracts, invading the periphery of the lobules, from a case of early biliary cirrhosis following infective hepatitis (× 160)

FIG. 2*a*. Liver in fulminant hepatitis

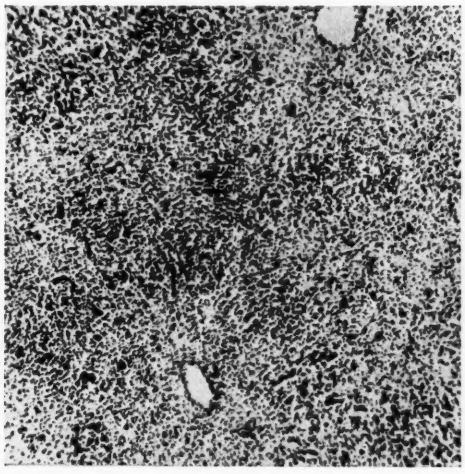

FIG. 2*b*. Fulminant hepatitis. Microscopic picture of the liver in Fig. 2*a* (× 48)

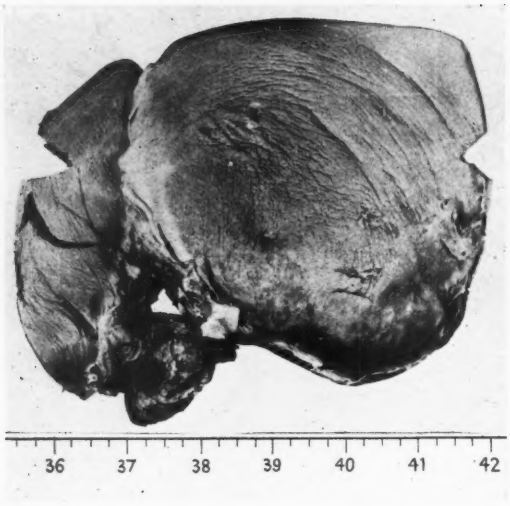

FIG. 3*a*. Liver in acute massive necrosis. The whole left lobe and the greater part of the right lobe are necrotic, where the capsule is wrinkled

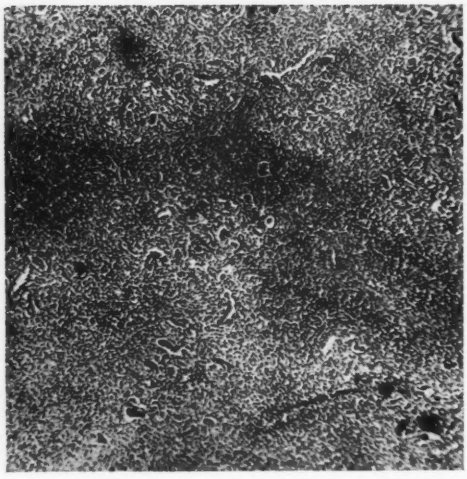

FIG. 3*b*. Extensive areas of necrosis where the bile-ducts are prominent (× 48)

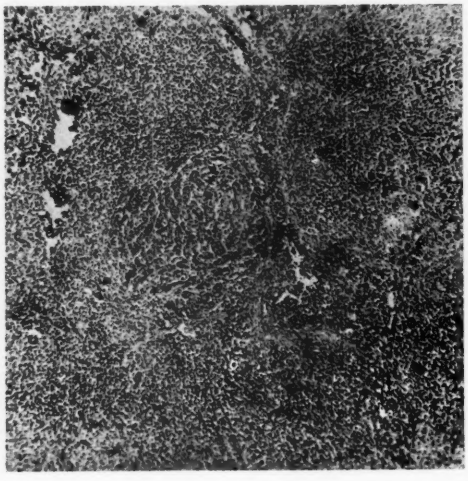

FIG. 3*c*. Group of liver cells which have escaped in the midst of extensive areas of necrosis (× 48)

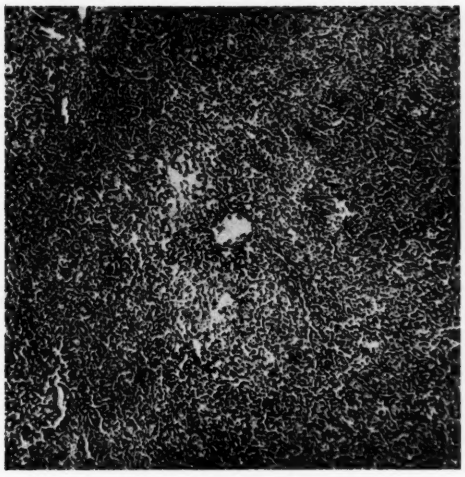

FIG. 3*d*. Lobules with normal architecture but centrilobular necrosis in intact areas of the same liver (Figs. 3*a*, *b*, *c*) (× 80)

FIG. 4*a*. Liver in subacute necrosis. The lighter areas contained surviving and proliferating liver cells, the darker areas condensed reticulin with no liver cells

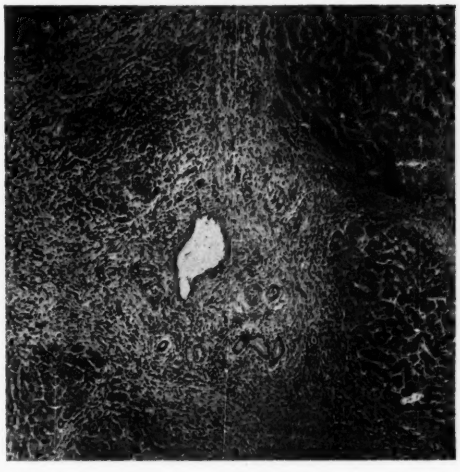

FIG. 4*b*. Section showing hyperplastic nodules and areas of condensed reticulin (× 48)

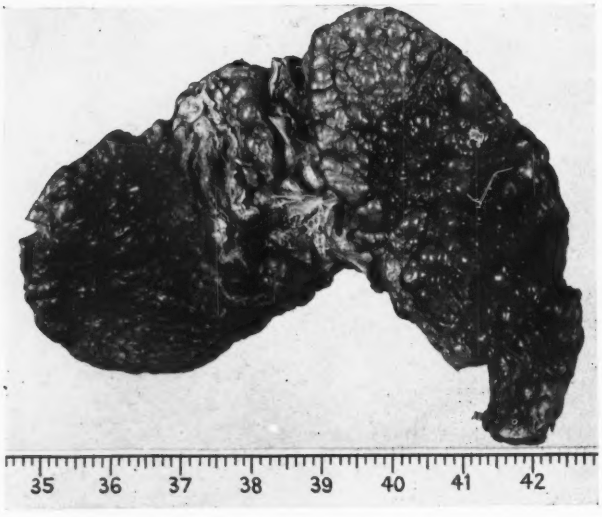

FIG. 5*a*. Liver in toxic cirrhosis (nodular hyperplasia). Some nodules are about 2 cm. in diameter, others much smaller

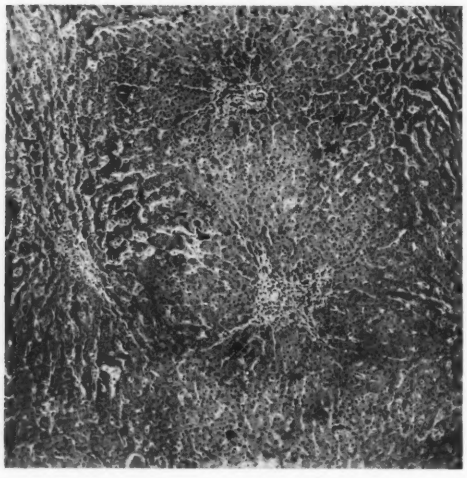

FIG. 5*b*. Toxic cirrhosis. Group of normal lobules (× 48)

FIG. 5c. Toxic cirrhosis. Condensed reticulin tissue surrounding hyperplastic nodules (× 48)

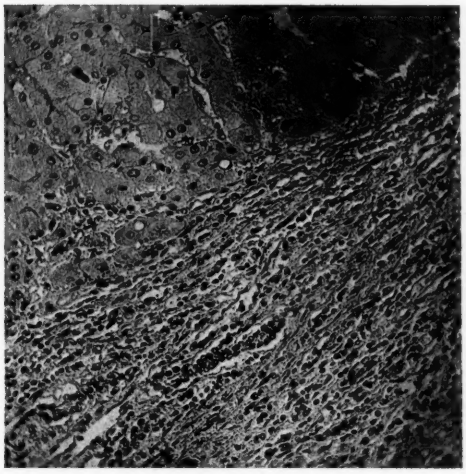

FIG. 5d. Toxic cirrhosis. High-power view of areas of scarring adjacent to liver cells

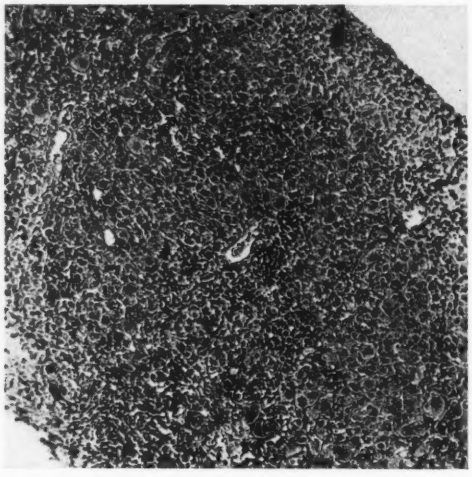

FIG. 6*a*. Biopsy of liver from a patient with infective hepatitis on the 20th day, showing cellular infiltration in portal areas (× 80)

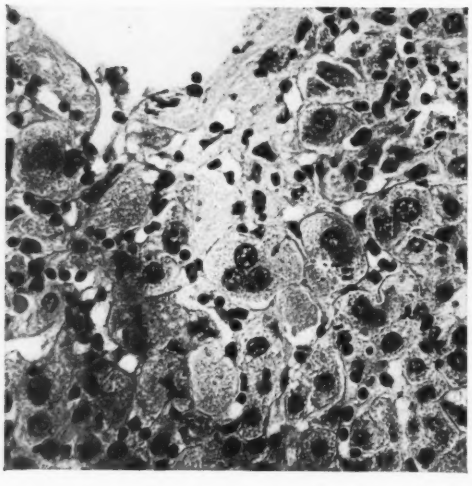

FIG. 6*b*. High-power view of the region near a central vein from the same specimen, showing regenerating liver cells (× 336)

616.8–009.831:616.36

OBSERVATIONS ON THE SYMPTOMATOLOGY AND PATHOGENESIS OF HEPATIC COMA[1]

By J. M. WALSHE

(From The Medical Unit, University College Hospital, London)

With Plate 38

THE association of jaundice with severe mental changes has been known from the time of Galen, who observed ' . . . bilis ad caput recurrens delirii causa'. The earliest account of a case of acute yellow atrophy has been attributed to Franciscus Ruboeus (1660); other early descriptions were collected by Morgagni (1761) from the writings of Baillou, Guarinonius, and Valsava. All these cases showed jaundice followed, after a matter of days or weeks, by convulsions, coma, and death. Other early accounts of acute fatal jaundice with mental and neurological changes are given by Griffin (1834), Bright (1836), and Budd (1845). The case reported by Bright is of particular interest because it includes a number of features that must be recognized as typical of hepatic coma, namely dilatation of the pupil, irregular jerky movements of the limbs, difficulty of articulation, flexion of the knees against the abdominal wall, and attacks of screaming followed by coma and death. Frerichs (1860), who may be said to have initiated the modern scientific study of liver disease, noted the gravity of delirium as a symptom of jaundice, and gave an analysis of the symptom-complex in a series of 31 cases of acute liver failure. Delirium, extreme violence, convulsions, muscular twitchings, trismus, tetany, hiccoughing, and grating of the teeth were all observed by him, and he also recorded dilatation and immobility of the pupils and, in one instance, yellow vision. Mossé (1879) and Bastian (1886) also recorded many of these signs, Bastian adding tonic spasm and profuse sweating in fatal jaundice.

In reviewing the modern literature certain general features may be noted. For example, though there is a wide range of clinical pictures of disordered function of the central nervous system, such changes as may accompany them in the brain must be reversible, since when recovery ensues there remain no signs of residual damage. The illness tends to be more acute in children than in adults, a fact which suggests that the nervous system in the former is more susceptible to the noxious factors concerned. Finally, as all observers since the time of Rokitansky have agreed, the brain in fatal cases does not show changes adequate to account for the symptoms observed during life. Similarly no significant abnormalities have been found in the cerebrospinal fluid. All the individual neurological signs reported in the present paper have been noted by earlier observers, some by one and some by another, and a number of pictures

[1] Received March 21, 1951.

of the varying syndrome of hepatic coma are to be found in the literature. It is hoped here to build up a complete picture of the disease process from its inception to death or recovery, and to record the changes which occur in consciousness and reflex activity. The earliest report of reflex changes in hepatic coma was made by Rolleston (1912), who observed that an extensor plantar response was sometimes present. Willcox (1919) found ankle clonus in some cases of fatal hepatitis; Elliott and Walshe (1925) confirmed the findings of an extensor response in cases of acute yellow atrophy, terminal cirrhosis, and carcinomatosis of the liver. Spence and Ogilvie (1927) and Snell and Butt (1941) emphasized the greater severity of such symptoms in children compared with adults, and recorded a peculiar 'cholaemic crying' and cranial nerve palsies. Greene (1941) and Lichtman (1949) drew attention to the differences between the coma of acute liver failure and that of cirrhosis. In the latter case the picture is one of the insidious onset of lethargy and coma, as compared with the personality changes, mania, and convulsive movements often found in the former. To the acute symptom-complex Himsworth (1947) added nightmares as of the gravest prognostic significance. Lucké (1944) and Lucké and Mallory (1946) also recorded increased reflex activity and personality changes in fatal epidemic hepatitis. Stokes, Owen, and Holmes (1945) described the neurological changes in acute hepatitis in some detail. They noted increased muscle tone, exaggerated tendon-jerks, choreiform movements, and Parkinsonism. In a small number of cases there were localizing signs following a focal haemorrhage in the brain. The clinical picture was later amplified by Stokes and Miller (1947), and the finding of normal cerebrospinal fluid and minimal histological changes in the brain was also reported. Adams (1949) reported disturbances of personality and of consciousness, rigidity, tremors, increased tendon-jerks, and forced grasping. A histological examination of the brains of 40 victims of hepatic coma revealed no pathological changes capable of accounting for the observed signs. Murphy, Chalmers, Eckhardt, and Davidson (1948) observed that, apart from loss of consciousness, there was no characteristic physical sign or biochemical estimation which made it possible to distinguish the comatose from the non-comatose case of liver failure.

Case Reports

The present series consists of 18 cases of hepatic coma. Cases 1 to 12 were all examples of acute liver failure, the 'acute yellow atrophy' of the older writers. Of these, Cases 8 and 9 were somewhat less acute, since the duration of their jaundice was nine and 12 weeks respectively. Cases 13 to 16 were examples of coma following long-standing cirrhosis. In Case 14 the episode of terminal liver failure may have been due to an acute toxic hepatitis superimposed on an early cirrhosis. Case 17 suffered from seven months' obstructive jaundice due to carcinoma of the extrahepatic bile duct and massive secondary neoplastic involvement of the liver. Cholaemia appeared to be precipitated by paracentesis abdominis. Case 18 suffered from the Budd-Chiari syndrome, and passed into hepatic coma 10 days after a spleno-renal shunt had been performed for the

TABLE

Neurological Signs in 18 Cases of Hepatic Coma

The disease in Cases 1–12 was acute or subacute atrophy, in Cases 13–16 cirrhosis with terminal coma, in Case 17 massive bile-duct carcinoma, and in Case 18 cirrhosis and post-operative liver failure.

Case number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Personality changes in pre-coma	..	±	..	..	+	+	+	..	+	+	..	..	..	+	..	..	±	..
Extreme drowsiness	+	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..
Coma	..	+	+	+	+	+	+	+	+	+	+	..	+	+	+	+	+	+
Cholaemic crying	..	..	..	..	..	..	..	+	+	+	+	..	..	..	..	..	..	..
Flexion of knees to abdomen	..	+	..	..	..	..	..	+	+	..	..	..	+	+	..	..	..	..
Yawning and hiccoughing	..	..	..	..	+	..	..	..	+	..	..	..	+	..	..	..	..	..
Dilated pupils	..	..	..	..	+	+	+	+	+	+	+	..	..	+	..	..	..	+
Ocular palsies	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..
Yellow vision	..	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..	..	..
Roving movements of eyes	..	..	+	..	+	+	..	..	+	+	..	..	+	..	..	..	..	..
Sucking reflex	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..
Increased arm-jerks	..	..	..	..	..	+	..	..	..	..	..	..	..	±	..	±	+	..
Grasp-reflex	..	+	..	..	..	..	..	+	+	..	..	..	..	..	..	..	..	..
Increased knee-jerks	..	..	..	..	..	+	..	+	+	..	+	..	+	+	+	+	+	+
Knee clonus	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..
Ankle clonus	..	..	..	+	+	+	..	+	+	+	+	..	+	+	+	..	+	+
Extensor plantar response	+	..	+	..	+	+	+	+	+	..	+	+	+	+	+	+	..	..
Muscular twitching	..	..	..	..	+	..	..	..	+	+	..	..	+	..	..	+	..	..
Muscular spasms	..	..	+	..	..	..	..	..	..	+	..	..	..	..	..	..	..	..
Increased muscle tonus	..	..	+	..	..	+	..	..	..	+	..	..	..	..	..	+	..	..
Lead-pipe or cogwheel rigidity	..	+	..	..	..	..	..	..	..	+	..	..	+	..	..	..	..	..
Choreiform movements	..	..	..	..	..	..	..	..	+	+	+	..	..	..	..	..	..	..
Depressed tendon-jerks, Kernig's sign	..	..	..	..	..	..	..	..	..	..	..	+	..	..	..	..	..	..
Duration of jaundice before coma (days)	8	21	5	7	14	8	3	70	42	24	10	7	..	..	16	..	..	..
Duration of coma (days)	6	7	2	1	4	2	2	3	17	3	1	4	5	16	3	4	1	7
Recovery	+	..	..	..	..	..	..	..	..	..	..	+	..	..	..	+	..	..
Age in years	77	61	48	45	37	37	22	21	13	7	$1\frac{5}{12}$	14	65	43	34	63	61	51
Sex	F	F	F	F	F	M	F	F	F	F	F	M	F	M	F	F	M	F

The tendon-jerks in Cases 1 and 2 were absent before the onset of the illness, and therefore are not included in the table. Jaundice was not prominent in cases of cirrhosis in coma; the duration of the illness was, of course, considerable.

relief of ascites. In all cases, where practicable, a neurological examination was made daily, and in some cases more frequently. The results of the observations made are listed in the Table. As it is impossible to convey in tabular form an accurate impression of the clinical picture of hepatic coma, five cases are described in greater detail.

1. (*Case 11 in the Table.*) *Fulminant hepatitis in an infant.* A female child aged 17 months was admitted with a history of one week of anorexia and malaise and three days of jaundice. At the end of her first week in hospital she had a small blood-stained vomit, and for a short period after this became unrousable. She then passed into a state of wild delirium, with bouts of crying; she made choreiform movements with her hands and arms. After a few hours she sank into a quiet coma, with incontinence of urine, and with intense flushing and sweating. Neurological examination at this stage showed the child to be in profound coma, with widely dilated pupils which failed to maintain their reaction to light. There were frequent mouthing movements of the lower jaw. In the arms there was no abnormal tone, and no grasp-reflex (forced grasping). The abdominal reflexes could not be elicited. The knee-jerks were abnormally brisk, there was a transient left ankle clonus and bilateral extensor plantar responses. This stage lasted a few hours; the child then developed hyperpyrexia, and died shortly afterwards. Post-mortem examination showed massive haemorrhagic necrosis of the liver, with no evidence of commencing regeneration.

2. (*Case 9 in the Table.*) *Subacute hepatic necrosis in a child.* A girl aged 13 years was admitted with a history of six weeks' jaundice fluctuating in intensity, anorexia, malaise, and one week of abdominal distension. At this stage examination of the nervous system showed no abnormality. Six days later she became restless and there was some clouding of consciousness, with lid-retraction, widely dilated pupils, and a wild staring expression. The knee-jerks were abnormally brisk, and the plantar responses were extensor. The legs were held tightly flexed against the abdomen, and the wrists were flexed, with the fingers hyperextended in an athetoid position. Later in the same day she became noisy, uttering maniacal cries. The following morning she was rational, alert, and intelligent; but the pupils showed hippus, and the plantar responses were still extensor. Three days after this episode all abnormal neurological signs had disappeared. After a further period of three days consciousness again became clouded. There were choreiform movements of the arms and drawing up of the knees to the abdomen. Muscular twitchings and hippus were present, and the plantar responses were again extensor. Two days later she became incontinent of urine, and began to hiccough. On the 18th day after admission there was a remarkable mental change: while consciousness remained altered, the child ceased to be querulous and became quite happy, giggling, laughing, and declaiming how well she felt. Later she became extremely noisy and restless, requiring sedation. The following day she was wildly irrational, passing through phases of intermittent coma and delirium; speech was incoherent, and there was a continuous low moaning. She again adopted the posture of crossing her legs and drawing her knees tightly against the abdominal wall, strongly resisting any attempt to extend her legs. On the following day, the 20th day in hospital, this state of affairs persisted, and in addition she was making determined attempts to kick off the bed-clothes; her pupils were contracted, she rolled her eyes, and yawned continuously. The arms displayed irregular choreiform movements. Increased knee-jerks, ankle clonus, and extensor plantar

responses were present. By the 21st day she was, for the first time, in unrousable coma. She maintained her sitting posture, with crossed flexed legs. The pupils were again widely dilated, the arm-jerks were exaggerated, and wild choreiform movements and forced grasping were present. The knee- and ankle-jerks and the plantar responses remained unchanged. The subsequent course was one of deepening coma, with muscular flaccidity, and death occurred on the 24th day. Post-mortem examination revealed extensive necrosis of the liver, with multiple regeneration nodules, themselves showing necrotic changes.

3. (*Case 2 in the Table.*) *Homologous serum jaundice.* The patient, a married woman aged 61 years, was a diabetic. Eighty-nine days after a blood transfusion administered at the time of an abdomino-perineal resection of the rectum she developed malaise, anorexia, and nausea, shortly followed by extreme lassitude and jaundice. After a week in this condition she was admitted to hospital. Neurological examination at this stage revealed peripheral neuritis, with loss of knee- and ankle-jerks. For 10 days her condition remained unchanged; she then developed high fever, abdominal distension, and skin petechiae. She became drowsy and querulous, resenting interference. Two days later she passed quietly into coma, with restlessness at night. During the day she lay quite still, with her knees drawn tightly up against her abdomen, and resisted attempts at examination. The arm-jerks were brisk, the knee- and ankle-jerks were absent, and the plantar responses were flexor. The pupils were normal. Fifteen days after admission to hospital she showed forced grasping and cogwheel rigidity in both arms. She died in deep coma. Post-mortem examination revealed extensive centrilobular necrosis of the liver, with no evidence of regeneration.

4. (*Case 13 in the Table.*) *Cirrhosis of the liver; cholaemia.* A married woman aged 65 years had suffered from abdominal swelling and mild jaundice for four months. After a paracentesis she became irrational and incontinent of urine for about 24 hours before passing into light coma. Neurological examination showed the patient lying quietly in bed with the legs drawn tightly to the abdominal wall; the pupils were dilated and reacted poorly to light. The arm-jerks were not remarkable, and there was no forced grasping. The knee-jerks were brisk, there was prolonged ankle clonus, and flexor plantar responses. Coarse fasciculations could be observed in the thigh muscles. The following day coma appeared to be deeper, and she no longer reacted to pain by withdrawing the stimulated limb. There was frequent yawning, and a sucking reflex was present. The arm-jerks were normal; lead-pipe rigidity was present, but not forced grasping. The knee-jerks were abnormally brisk, and there were transient ankle clonus and bilateral extensor plantar responses. Intense rigidity was present in the legs, which were held extended and crossed. On the third day the only change in these signs was a return of the prolonged ankle clonus. Thereafter the patient sank into steadily deepening coma, and died on the fifth day. Post-mortem examination revealed a deeply scarred liver, much reduced in size, and showing histologically post-necrotic scarring with extensive areas of parenchymal necrosis.

5. (*Case 12 in the Table.*) *'Acute yellow atrophy'; recovery.* A boy aged 14 years, one week before his admission, had fallen heavily on to his right side, the fall causing considerable upper abdominal pain. Two days later he became feverish, and complained of continuous severe pain in the right upper abdomen, nausea, anorexia, and vomiting, frontal headache, photophobia, and dizziness on sitting up. He was constipated and was passing dark urine. For the next four days he was given penicillin by his doctor, with no improvement. He was therefore

referred to hospital, and was admitted to a surgical ward for observation. Physical examination at that time showed tenderness over the liver, no evidence of intraperitoneal haemorrhage, light icterus, and bilateral extensor plantar responses. Two days later he was transferred to a medical ward. Examination showed a severely ill boy lying turned away from the light, with a temperature of 100° F., and a pulse-rate of 50. Neurological examination revealed photophobia, neck rigidity, Kernig's sign, depressed tendon-jerks, and a left-sided extensor response. The following morning he was somewhat improved, and both plantar responses had become flexor. In a further 24 hours the boy was obviously recovering. The combination of extreme drowsiness with the abnormal neurological signs and the considerable elevation of the aminoacid levels found in both blood and urine were thought, initially, to be of the gravest possible prognostic significance.

In no case in the present series has a detailed histological study of the brain been carried out, but in cases examined *post mortem* no macroscopic evidence of raised intracranial tension, or of a local lesion in the brain, has been found.

Summary of Clinical Observations

Before attempting to review the theories put forward at various times to account for the symptomatology of hepatic coma, it is necessary to consider which elements of the nervous system are principally affected, and in what order of frequency. Reference to the Table shows that, apart from loss of consciousness, there is no single feature common to every case in this series. Most patients passed through a brief period of confusion before the onset of coma, but true personality changes lasting one or more days were rare except in cases of acute liver failure. One patient (Case 6) was admitted from a mental observation ward, where he had been sent because of 'truculence, violence, and dirty habits'. Personality changes were either followed or replaced by a period of wild delirium which, again, was only observed in cases of acute liver failure. This was particularly the case in children and young adults. Both loss of consciousness and personality changes must be regarded as indicative of a widespread disturbance of cortical function. While in coma, and apart from reflex changes, the patients often showed certain characteristic signs. Perhaps the most remarkable was the adoption of a position in which the legs were crossed and tightly drawn up to the abdomen; this sign was observed in both acute and chronic liver failure. Yawning and hiccoughing also occurred, both in the stage of pre-coma and in coma. It is possible that the hiccoughing was due to diaphragmatic irritation from perihepatitis. In the cranial nerves abnormal signs were not commonly observed, except dilatation of the pupils and hippus, which were seen rather more commonly in the acute than in the chronic cases. Next to coma, pyramidal signs were the most commonly observed neurological abnormality. Spasticity and muscular spasms were found occasionally in the coma of acute liver atrophy, as also was tonic grasping. Abnormal arm-jerks were rare. Increased knee-jerks were common in hepatic coma of all types, as were extensor plantar responses and ankle clonus. In one case a prolonged knee clonus was observed, and in another the extensor plantar response could be elicited from a wide field on both legs. It is of some interest that an ankle

clonus commonly develops before the plantar response becomes extensor; it may even be present in the stage of pre-coma, and in cases in which an extensor plantar response is never found, however carefully and frequently sought. It is believed that this combination of ankle clonus and plantar flexor responses occurs in no other organic condition except amyotrophic sclerosis in its earlier stages. A unilateral extensor plantar response was seen occasionally as a transient phenomenon. Signs attributable to the basal ganglia were also observed, as illustrated by choreiform movements and athetoid postures; these signs were noted in all three children included in the present series, but in no adult case. 'Lead-pipe' and 'cogwheel' rigidity were both found in the later age-groups. Extrapyramidal signs were recorded both in company with, and apart from, pyramidal signs. All three children and one young adult also passed through periods of noisy delirium, presumably the 'cholaemic crying' of Spence and Ogilvie (1927). Although muscular twitchings, or rather coarse fasciculations and increased myotatic irritability, were observed in five cases, in no case did convulsions occur. In one case, in which recovery occurred, there were signs of meningeal irritation, as evidenced by photophobia, neck rigidity, and depressed tendon-jerks; extensor plantar responses were also present, that on the right returning to a flexor response about 24 hours before that on the left.

In the present series routine biochemical estimations threw no further light on the problem under review. Plasma-proteins, prothrombin concentration, and serum-bilirubin levels varied widely; in one case the blood-urea rose during the course of coma from 24 mg. to 96 mg. per 100 ml., and in another case from 54 mg. to 100 mg. per 100 ml. In no case was it possible to demonstrate hypoglycaemia, the lowest blood-sugar level recorded being 67 mg. per 100 ml. The cerebrospinal-fluid sugar was estimated quantitatively in two cases, and was 70 mg. per 100 ml. in one case and 160 mg. per 100 ml. (duplicate reading) in the other. Estimation of the inorganic ions potassium, sodium, chloride, and phosphate all gave readings within the limits of normal. The plasma CO_2-combining power showed a tendency to fall, but never reached severely acidotic levels. Estimation of the plasma amino-nitrogen was not carried out as a routine, but a number of readings were obtained, the highest in a case of acute liver failure being 20 mg. per 100 ml. and the highest in a case of cirrhosis 9·46 mg. per 100 ml.; the latter reading was synchronous with a blood-urea of 100 mg. per 100 ml. The application of two-way paper chromatography to clinical problems (Dent, 1949) has made it possible to study aminoacid metabolism in greater detail than in the past. By this method an abnormality in the concentration of a single aminoacid in the blood or urine can be detected even when the total concentration of α-amino-nitrogen is normal. It has thus been possible in the present series of cases to study day-to-day variations in the urinary aminoacid pattern, and in a number of cases to study the blood and cerebrospinal fluid patterns. In a preliminary communication Dent and Walshe (1951) reported that, even in apparently mild cases of liver injury, abnormalities in the metabolism of one or more aminoacids could occur, and that the abnormality increased with the severity of the illness to the grossly abnormal patterns

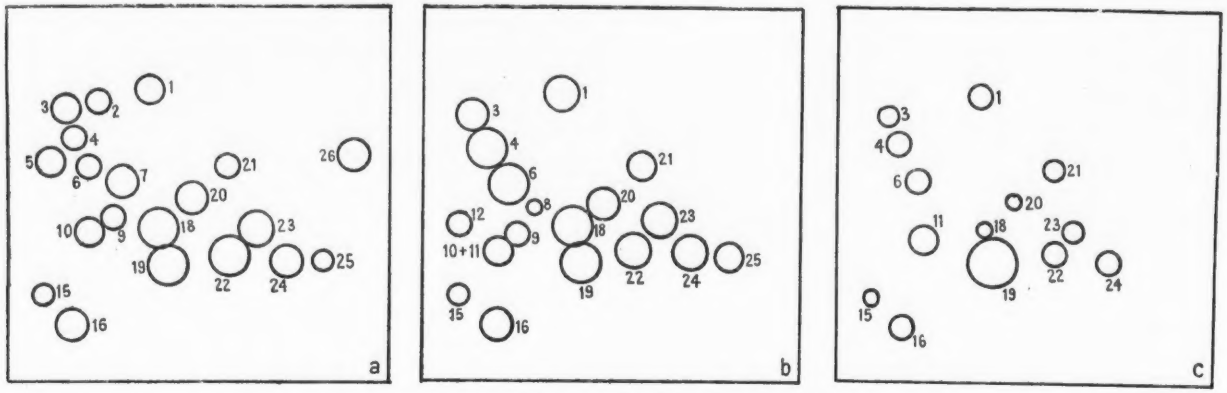

FIG. 1. Acute yellow atrophy of the liver (Case 11).

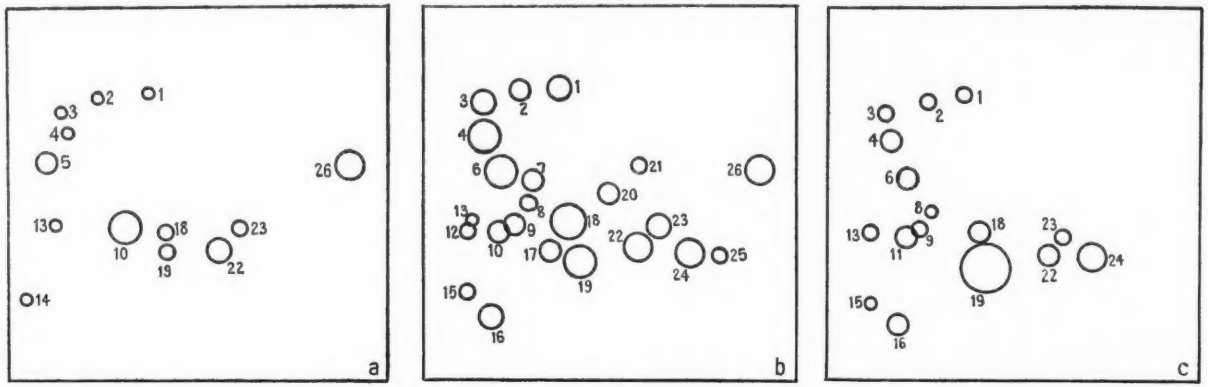

FIG. 2. Cirrhosis of the liver with coma (Case 13).

(*a*) 50 μl. urine, oxidized; (*b*) 625 μl. plasma ultrafiltrate, oxidized; (*c*) 625 μl. cerebrospinal fluid ultrafiltrate, not oxidized.

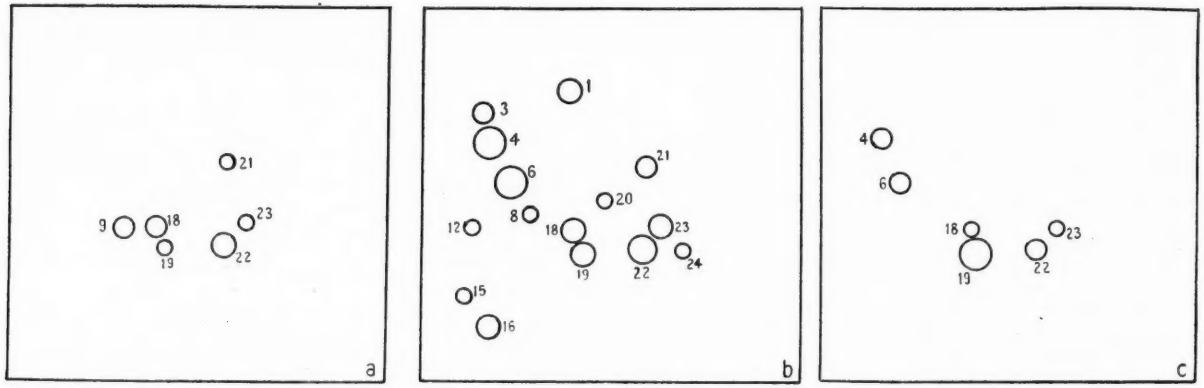

Fig. 3. Normal control.

(*a*) 50 μl. urine, oxidized; (*b*) 625 μl. plasma ultrafiltrate, oxidized; (*c*) 625 μl. cerebrospinal fluid ultrafiltrate, oxidized.

Figs. 1, 2, 3. Diagrams of chromatograms of plasma, urine, and cerebrospinal fluid from a case of acute yellow atrophy of the liver, a case of cirrhosis of the liver in coma, and a normal control. The sample has been placed at the bottom right hand corner of the paper. Phenol has been run from right to left as the first solvent, collidine-lutidine upwards as the second solvent. The circles indicate the aminoacids in their final positions as revealed after treating the paper with ninhydrin. An arbitrary scale has been used in which the sizes and intensities of the aminoacid spots are represented by the sizes of the circles.

1, tyrosine; 2, tryptophan; 3, phenylalanine; 4, leucine or isoleucine, or both; 5, ethanolamine; 6, valine; 7, methionine sulphone, from methionine; 8, α-aminobutyric acid; 9, histidine; 10, β-aminoisobutyric acid; 11, methionine sulphoxide; 12, proline; 13, methylhistidine; 14, fast-arginine, an unidentified substance; 15, arginine; 16, lysine; 17, citrulline; 18, alanine; 19, glutamine; 20, threonine; 21, taurine; 22, glycine; 23, serine; 24, glutamic acid; 25, aspartic acid; 26, cysteic acid, from cystine.

The sulphur-containing aminoacids methionine and cystine are normally demonstrated chromatographically after they have been oxidized by H_2O_2 to methionine sulphone and cysteic acid respectively. The pathological specimens of cerebrospinal fluid are here shown unoxidized to demonstrate the presence of methionine in the abnormal state as methionine sulphoxide.

and concentrations, involving many aminoacids and lasting over several days, which are found in acute yellow atrophy. They reported finding a number of abnormal patterns in the urine of patients with different types of liver disease. These patterns fell into the following groups: first, an excess of all the common aminoacids in high concentration, and possibily the presence of certain rare or unidentified aminoacids, this picture being found in acute liver failure; second, an excess of many aminoacids with a small rise in concentration, as found in acute infectious hepatitis; third, an excess of cystine, alone or in association with a limited number of other aminoacids—commonly β-aminoisobutyric acid, methylhistidine and taurine—varying with the severity of the illness, this picture being found in chronic liver disease and infiltrations of the liver. They also suspected the presence of two other groups, one involving the aromatic aminoacids and one of the variants of group three, and the second involving methionine and one of the variants of group three. More recent studies have confirmed this view. Detailed findings were also given from a case of acute hepatitis, showing the considerable day-to-day variations of pattern that may occur. The urine from 15 of the 18 cases in the present series was subjected to chromatographic analysis, and the findings are summarized below.

1. Gross aminoaciduria of acute yellow atrophy: Cases 3, 4, 5, 6, 7, 9, 11, 12.
2. Weak acute yellow atrophy pattern: Cases 1, 10, 17.
3. Abnormal pattern affecting principally cystine, β-aminoisobutyric acid, and γ-aminobutyric acid: Cases 2, 8, 13, 18.

In Case 2 the urine was so heavily infected that the findings are of doubtful significance. In Case 8 there was severe oliguria with the onset of coma, so that the urinary pattern, as was shown in Case 13, may not have reflected the true state of affairs existing in the plasma. The finding of a raised plasma α-amino-nitrogen, or of an abnormal plasma-aminoacid pattern, in those cases in the present series in which plasma analyses were carried out, differentiates them from cases of aminoaciduria resulting from a low renal threshold, as in the Fanconi syndrome (Dent, 1947) or cystinuria (Dent and Rose, 1949, 1951). The plasma from five cases was examined (Cases 1, 4, 11, 12, and 13) and in all the concentration was elevated and the pattern abnormal (Figs 1, 2, 3). In Cases 11, 12, and 13 the cerebrospinal fluid was also examined, and was free of bile. In all three the aminoacid concentration was high and the pattern was abnormal, the abnormality being greatest in the case with the most severe clinical picture. The most striking abnormality of pattern was the excess of glutamine; normally the dominant aminoacid in the fluid, it was here found in relatively greater excess than normal. In Cases 11 and 13, who were in deep and fatal coma, glutamic acid was, to a less extent, also present in excess, and in both cases methionine sulphoxide was detected, in Case 13 in low and in Case 11 in moderate concentration. Neither methionine nor its sulphoxide is chromatographically detectable in normal cerebrospinal fluid in the volume (625 μl.) used for analysis; methionine sulphoxide has not previously been reported as occurring spontaneously in body fluids (Dent, 1948), and its detection is a surprising abnormality. It must be mentioned, however, that despite

all precautions it is possible that this finding of the sulphoxide is an artefact due to oxidation of methionine during the preparation of the chromatograms. Case 12, on the other hand, who was drowsy but not in coma, and whose tendon-jerks were diminished, not exaggerated, showed far less severe changes in the fluid, although the concentration of aminoacids in the blood was comparable to that in Case 11. Chromatograms of synchronous specimens of blood, urine, and cerebrospinal fluid from one case of acute liver failure (Case 11) and from one case of cirrhosis (Case 13) are shown in Figs. 1 and 2, together with a set of normal controls for comparison (Fig. 3). Figs. 4–7 (Plate 38) are photographs of chromatograms illustrating the disappearance of aminoacids from the urine of Case 12 during a period of 48 hours, during which the neurological abnormalities resolved.

Discussion

No entirely satisfactory explanation of the manifestations of hepatic coma has as yet been put forward, and no biochemical estimation is known that will give an indication of the prognosis in a given case. The absence of a structural basis, that is of a discoverable histological lesion, to account for the neurological signs of hepatic coma has already been noted in the introduction, and this observation appears to rule out the possibility of a virus infection of the brain (Stokes and Miller, 1947; Lucké, 1944; Lucké and Mallory, 1946). Exception must be made of a small percentage of cases in which localizing signs follow a focal haemorrhage in the brain (Stokes and Miller, 1947; Lucké, 1944). The two cases described by Byrne and Taylor (1945) may also have belonged to this category, but no pathological studies are available. Such haemorrhage may be related to the reduced prothrombin concentration often found in fatal hepatitis. The possibility that hypoglycaemia may play a part in producing the symptom-complex of hepatic failure was suggested by Frerichs (1860), but Elliott and Walshe (1925) observed reflex changes in both acute and chronic liver failure in the presence of a normal blood-sugar level; this fact has more recently been emphasized, or implied, by Roman (1927), Spence and Ogilvie (1927), Greene (1941), Snell and Butt (1941), Lichtman (1949), and Murphy, Chalmers, Eckhardt, and Davidson (1948), and is all the more remarkable in view of the work of Mann (1927), who showed that after total hepatectomy the dog dies in three to eight hours of hypoglycaemia unless kept alive with glucose. It appears probable that cases of cholaemia pass through a phase of convulsions only if there is hypoglycaemia. Certain authors have attempted to explain the neurological signs as due to an intestinal toxin absorbed from the gut and allowed to pass through a damaged liver to enter the systemic circulation (Lucké, 1944; Stokes, Owen, and Holmes, 1945; Baker, 1948). Support for this theory comes from the work of Baló and Korpassy (1932) who, by feeding lean meat to dogs with Eck fistulae, were able to produce a non-suppurative encephalitis localized to the caudate nucleus. This encephalitis, they concluded, was due to a short-circuiting of the liver from the portal circulation. Relief of symptoms followed promptly on stopping the diet. Before accepting the

theory of an intestinal toxin, it must be remembered that no claim has been made that this toxic factor is an abnormal product of digestion, or that the intestinal mucosa has become abnormally permeable. The implication of this work appears to be that a product of intestinal fermentation, which is normally detoxicated in the liver, is allowed to pass through a damaged organ and so reaches the brain. If this were so every case of hepatic cirrhosis and portal hypertension subjected to a porto-caval shunt or to a spleno-renal anastomosis should develop a striatal syndrome. An entirely new approach to the problem was opened by McArdle (1940) when he reported a fall in the plasma pseudo-cholinesterase in 79·5 per cent. of cases of parenchymal liver disease. In a discussion on plasma cholinesterase levels in liver disease (Fifth Conference on Liver Injury, 1946, Macey Foundation, New York) Wescoe confirmed McArdle's findings. Labby suggested that many of the symptoms of patients with liver damage may be due to an accumulation of acetylcholine in the blood following a fall in the plasma esterase. However, Wescoe pointed out that he was able to destroy the plasma cholinesterase of patients with liver disease by the injection of 2 mg. of DFP without increasing the severity of their symptoms. Furthermore, like Augustinsson (1948), he did not believe that the plasma cholinesterase was involved in neuromuscular conduction. Kunkel supported this view and reported that, by an infusion of an esterase-free fraction of human albumin, he was able to produce symptomatic improvement in patients with hepatic cirrhosis without raising the plasma esterase level. Moreover it is possible, by the infusion of human serum rich in cholinesterase, to raise the plasma esterase level to within normal limits without materially affecting the depth of consciousness of patients in hepatic coma (A. Wilson and J. M. Walshe, unpublished observations). Certain writers have attributed a toxic action to the products of hepatic autolysis (Frerichs, 1860; Spence and Ogilvie, 1927; Heyd, 1943), and there is experimental work on animals to support this view. Heyd (1943) believed that the products of liver death can produce hyperpyrexia and coma, with permanent renal damage as a sequel. Mason and Davidson (1924–5) showed that, if 30 to 110 gm. of the liver of a dog were resected and left free in the peritoneal cavity, death invariably ensued, usually within 16 hours. In such animals there was a terminal rise in the blood aminoacids. They considered these aminoacids to be potentially the most toxic of the various nitrogen constituents which might cause death by being liberated from the autolysing fragment. Mann (1927) observed that if the hepatic artery and vein of a dog with an Eck fistula are tied, the animal dies of hepatic insufficiency; if, on the other hand, the artery alone is ligated the animal will die in about half the time, because the products of liver autolysis are permitted to enter the systemic circulation. Snell and Butt (1941), who further explored the possible biochemical disorders in eight cases of hepatic coma, could find no significant alteration in the protein or electrolyte levels of the blood. There was a small increase of lactic acid in the blood in one case, and of pyruvic acid in two others. Lumbar puncture, performed on two patients, yielded a normal fluid. They suggested in conclusion that there was a breakdown of carbohydrate metabolism

due to a failure of enzyme action. In patients who recovered from coma there was no residual damage to the nervous system. This supported their theory of an unknown biochemical lesion. Amatuzio and Nesbitt (1950) also investigated the pyruvate levels in the blood, urine, and cerebrospinal fluid of normal controls, of patients with liver disease without coma, and of patients with liver disease in coma. They found a significant rise in the pyruvate levels in the third category. When there was recovery from coma the pyruvate level returned to normal. They believed that there was a failure of the liver to take up pyruvic acid to form the dicarboxylic acids necessary for the Krebs cycle, and they suggested that this deficiency might lead to a failure of cellular aerobic metabolism. They offered no suggestion as to why the picture of hepatic coma is so different from that found in other conditions in which the blood pyruvate level is raised, namely aneurin deficiency, alcoholic polyneuritis, thyrotoxicosis, congestive heart failure, and the effect of severe exercise. Particular attention was paid to aminoacid metabolism by Stadie and Van Slyke (1920), who studied a single case of acute yellow atrophy, and showed that the liver protein underwent autolysis and was converted to aminoacids and peptides. They concluded that only about 60 per cent. of the excess of aminoacids was deaminated to urea, instead of the usual 85 to 90 per cent. They also observed an increased percentage of urinary amino-nitrogen, an increased excretion of ammonia, and a small fall in the plasma-bicarbonate. The blood-urea remained normal. They did not find similar changes in cases of hepatic cirrhosis with coma. Roman (1927) and, more recently, Greene (1941) also commented on the normal blood aminoacid levels found in cases of cirrhosis, as compared with the very considerable elevation that may occur in acute liver failure. Greene went so far as to say that there are no significant changes in the blood chemistry of patients with cirrhosis dying of hepatic insufficiency. He concluded that there is no specific toxin, and that the syndrome is probably due to a failure of the manifold activities of the liver. Murphy, Chalmers, Eckhardt, and Davidson (1948) also concluded that there is no characteristic finding in the blood or spinal fluid of patients with cirrhosis in coma. They also recorded that it was not possible to alter the depth of consciousness by the intravenous injection of benzedrine or caffeine.

Any theory which attempts to account for the symptom-complex of hepatic coma must provide a possible explanation of the following facts:

1. All signs and symptoms are potentially, and sometimes very rapidly, reversible.
2. The clinical picture and reflex changes are subject to a wide degree of variation from day to day and from case to case.
3. There are no macroscopic or significant microscopic changes in the brain.
4. The analyses of plasma and cerebrospinal fluid so far reported show no constant changes adequate to account for the signs and symptoms.
5. A clinically indistinguishable coma may occur either in acute hepatic necrosis or in cirrhosis.

It is reasonable to conclude from these facts that hepatic coma is of biochemical origin. In the past, attempts to attribute a toxic action to abnormal aminoacid metabolism in hepatic coma have broken down on the frequent finding of a normal total α-amino-nitrogen in the plasma of patients in coma due to hepatic cirrhosis. In all cases investigated in the present series an abnormal pattern of aminoacids was found in the urine (15 cases), in the blood (5 cases), and in the cerebrospinal fluid (3 cases). These findings suggest that the neurological syndrome of hepatic failure may be due to a disturbance of the metabolism of one or more aminoacids following (1) a breakdown of the liver mechanism for regulating plasma-aminoacid levels, and (2) the liberation of potentially toxic amounts of certain aminoacids and peptide compounds from the autolysing liver. Estimation of the total plasma α-amino-nitrogen will not necessarily reveal such a disturbance, because considerable variations in the pattern of blood amino-acids and of urinary aminoacid excretion can occur without a significant change in the total amino-nitrogen level. The fact that such variations occur in the urine from cases of liver disease has been demonstrated by Dent and Walshe (1951). Evidence that disturbance of aminoacid balance in experimental animals can be toxic is plentiful. Moreover, Cannon (1948) has shown that if key aminoacids are not all available to the body at the same time there will be a failure of protein synthesis. Such a failure may lead to further fluctuations of the aminoacid pattern in the blood. That individual aminoacids can be toxic when present in excess has been amply demonstrated by experiment. Mann (1927) showed that the dog after hepatectomy could not tolerate infusions of glycine or alanine which produced no symptoms in the normal animal. Madden, Woods, Shull, Remington, and Whipple (1945) showed that, in dogs, the addition of glutamic acid to an intravenous injection of various synthetic mixtures of crystalline aminoacids produced vomiting. Ni (1937) showed that, by feeding an excess of glycine to guinea-pigs, it is possible to produce loss of muscle tone, paralysis, and death. Excess of cystine can produce haemorrhagic necrosis of the liver (Earle and Victor, 1942); excess of serine can produce tubular necrosis of the kidney (Morehead, Fishman, and Artom, 1945). Moreover, the toxic factor of agenized flour which produces canine hysteria (Mellanby, 1946) is itself probably derived from methionine (Campbell, Work, and Mellanby, 1950). In man, the intravenous infusion of protein hydrolysates has produced nausea, vomiting, hyperpyrexia, vasodilatation, abdominal pain, and convulsions (Report of the Council on Pharmacy and Chemistry, 1948). A possible example of the toxic action of a single aminoacid in man is suggested by the syndrome of phenylpyruvic oligophrenia, in which only one aminoacid, phenylalanine, has been found in excessive concentration in the blood and cerebrospinal fluid (Jervis, Block, Bolling, and Kanze, 1940; Jervis, 1947). Dent and Lindan have confirmed this observation by chromatographic methods, and have shown that no other aminoacids are involved (private communication).

It was shown by Quastel and Wheatley (1932) that glutamic acid is slowly metabolized by the brain, and by Krebs (1935*a*) that it will combine with ammonia to form glutamine. It has also been demonstrated that it is the only

aminoacid able to support brain respiration (Krebs, 1935*b*; Quastel, 1935; Weil-Malherbe, 1936). Mayer-Gross and Walker (1949) were able to restore consciousness to 26 of 45 patients in hypoglycaemic coma by the intravenous injection of 20 gm. of glutamic acid. In a recent review of the metabolism of glutamic acid by nervous tissue, Weil-Malherbe (1950) stated that glutamic acid takes part in three enzymic reactions in the brain, (1) amination, (2) transamination, and (3) amidation. He believed that these three reactions are probably all part of a single system for the removal of intracellular ammonia. This central role in the ammonia-binding mechanism he believed to be the primary function of glutamic acid in the central nervous system. In the process of deamination the first breakdown product of glutamic acid is α-ketoglutaric acid, which is itself concerned with pyruvate and therefore with carbohydrate metabolism (Weil-Malherbe, 1936). Finally Weil-Malherbe concluded that the role of glutamic acid in the supply of energy to the brain is secondary to its role in the ammonia-binding mechanism. In its ability to bind ammonia, to support brain respiration, and to alter the permeability of the cell-membrane to potassium ions, glutamic acid is unique. Clearly, if glutamic acid plays such a key part in cerebral metabolism, interference with any of these reactions may be expected to produce disturbances of cerebral function. The possible presence of methionine sulphoxide in the cerebrospinal fluid of two of our patients with hepatic coma suggests that such an interference may have occurred, since Waelsch, Owades, Miller, and Borek (1946) and Borek, Miller, Sheiness, and Waelsch (1946) have shown that methionine sulphoxide will inhibit glutamic acid metabolism in *Lactobacillus arabinosus*, probably by blocking the amidation of glutamic acid to glutamine. It is possible, therefore, that methionine sulphoxide may similarly interfere with glutamic acid metabolism in the brain. This interference may then give rise to a breakdown of the ammonia-binding mechanism, with a consequent accumulation of ammonia, itself a highly toxic substance. There may also be interference with carbohydrate metabolism (to abnormalities of which the brain is extremely sensitive) both by competition for adenosine triphosphate and by interference with the supply of α-ketoglutaric acid for the reaction glutamic acid ⇋ α-ketoglutaric acid ⇋ pyruvic acid. It is significant in this connexion that in all the cerebrospinal fluids examined there was an abnormal concentration of glutamine, and in one an abnormal concentration of glutamic acid. In the latter case there was also an abnormally high glucose concentration of 160 mg. per 100 ml., suggesting some interference with its utilization. It is not suggested that the mechanism indicated above offers a complete explanation of the varied symptomatology of hepatic coma, but it points to one way in which a disturbed aminoacid pattern in the blood could lead to a disturbance of cerebral function. Since there are other ways in which the aminoacid pattern has been found to vary during the course of the illness, so presumably may the abnormalities of brain metabolism vary. It is therefore suggested tentatively that changes in the aminoacid pattern of the body-fluids are capable of producing varying neurological syndromes which would be potentially reversible, would not be associated with macroscopic or

significant microscopic changes in the brain, and would not be detectable by any of the analytical methods used in the past.

In conclusion I wish to thank Professor M. L. Rosenheim for his advice and encouragement, Dr. C. E. Dent for assistance with the biochemical problems, Miss D. I. Fowler for the plasma α-amino-nitrogen estimations, and Mr. A. Bligh for the photographs. I also wish to thank the following members of the staff of University College Hospital for permission to publish cases admitted under their care: Dr. J. C. Hawksley, Dr. H. P. Himsworth, Dr. H. Nicholson, Professor M. L. Rosenheim, Dr. B. E. Schlesinger, and Dr. J. F. Stokes.

Summary and Conclusions

1. The literature describing the neurological manifestations of hepatic coma is reviewed.

2. The neurological signs observed in 18 cases of hepatic coma are described. The full picture consisted of personality changes, mania, and coma, with dilated pupils, choreiform movements of the arms, tonic grasping, and sometimes lead-pipe or cogwheel rigidity; absent abdominal reflexes, increased knee-jerks, ankle clonus, and extensor plantar responses. In some cases there was either spasticity or lead-pipe rigidity of the legs. During the early phase of coma the patients sometimes adopted a characteristic posture, with the legs tightly drawn up to the abdominal wall. Cranial nerve palsies were a rare accompaniment, and convulsions were not observed. All these changes were more prominent in children than in adults.

3. A number of theories to account for such changes have been advanced at various times. It is here suggested that hypoglycaemia may precipitate convulsions, but is not otherwise directly associated with the production of symptoms. The possibility of an intestinal toxin passing through a damaged liver to enter the general circulation is discarded; so also is the theory that acetylcholine accumulates in the blood as a result of a fall in the plasma-cholinesterase. Reference is made to experimental work which suggests that the products of autolysis of the liver parenchyma, which have a high aminoacid content, are toxic. It is possible that these products, entering the circulation, account for the phase of excitement observed in acute liver failure.

4. The theory is put forward that the disturbed pattern of blood aminoacids, which occurs as the result of both acute and chronic liver failure, may be toxic to the brain. Experimental work in animals which supports this theory is briefly referred to. It is suggested that the variable clinical picture of hepatic coma is almost certainly of biochemical origin, and may be directly related to the variable pattern of the blood aminoacids.

5. The part played by glutamic acid metabolism in the central nervous system is described. It is suggested that in some cases interference may have occurred in the utilization of this substance, with a consequent breakdown in the ammonia-binding mechanism of the brain. There may also have been a

disturbance of carbohydrate utilization, leading to the disturbances of consciousness and to the reflex changes which were observed.

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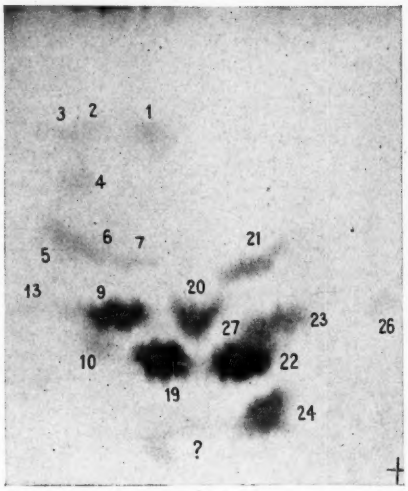

FIG. 4

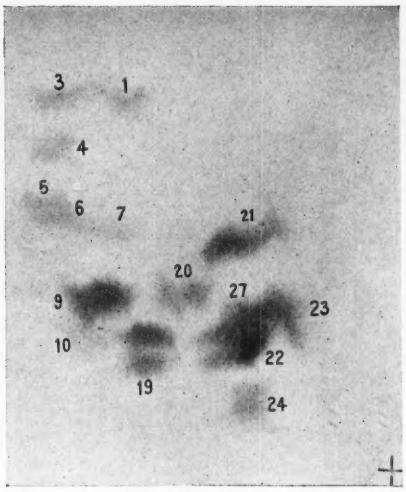

FIG. 5

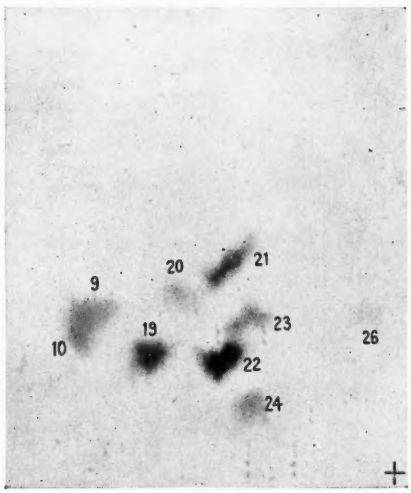

FIG. 6

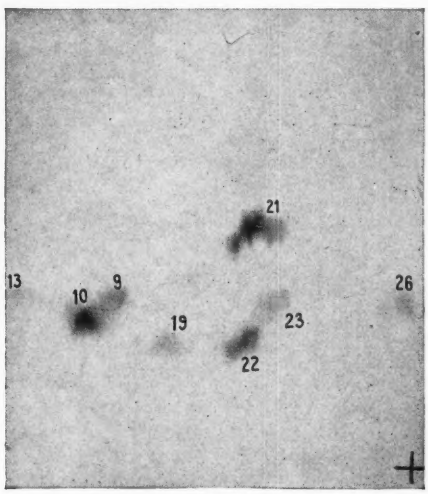

FIG. 7

FIGS. 4 to 7. Chromatograms of 50 μl. of urine, oxidized, collected at 12-hourly intervals from Case 12 during the phase of recovery from abnormal neurological signs.

1, tyrosine; 2, tryptophan; 3, phenylalanine; 4, leucine or isoleucine, or both; 5, ethanolamine; 6, valine; 7, methionine sulphone, from methionine; 9, histidine; 10, γ-aminoisobutyric acid; 13, methylhistidine; 19, glutamine; 20, threonine; 21, taurine; 22, glycine; 23, serine; 24, glutamic acid; 26, cysteic acid, from cystine; 27, asparagine.

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1951

FORTY-FIFTH ANNUAL GENERAL MEETING

THE FORTY-FIFTH ANNUAL GENERAL MEETING was held in Glasgow on Friday and Saturday, May 11 and 12, 1951, in the Chemistry Department Lecture Theatre of the University. The attendance book was signed by 188 members and 36 visitors. The proceedings began at 9.40 a.m.

The President, Sir John Parkinson, was in the Chair.

The Minutes of the last Annual General Meeting having been published in the *Quarterly Journal of Medicine* were taken as read, confirmed, and signed.

In his absence through sickness the *Treasurer's Accounts* were presented by the Secretary. The income and expenditure account for the year ending March 31, 1951 showed a balance carried forward of £611 as compared with a balance brought forward at the beginning of the year of £538. The position was not quite so favourable as would appear from these figures, because they included income-tax refunds and cash payments on conversion of securities totalling £129. It therefore seemed probable that the increase in subscription rate could not be delayed very much longer. On the capital side the Association's assets started the year with £3,347 and finished with £3,361, apart from the capital assets mentioned above.

The election of Officers, Executive Committee, Honorary Members, Extra-Ordinary Members, and Ordinary Members then followed.

Executive Committee

President. Professor Sir John McNee.

Treasurer. Dr. C. Newman.

Secretary. Dr. W. I. Card.

Members for England:

Professor R. E. Tunbridge.
Dr. K. Shirley Smith.
Dr. A. M. Cooke.
Professor R. Platt.
Professor R. V. Christie.
Dr. Terence East.

Members for Scotland:

Dr. W. R. Snodgrass.
Professor H. W. Fullerton.
Dr. J. D. S. Cameron.

Members for Ireland:

Dr. H. Hilton Stewart.
Dr. F. F. Kane.
Dr. D. K. O'Donovan.

Election of Honorary Member

Sir John Parkinson.

Election of Extra-Ordinary Members

Sir Harold Boldero.
Dr. Geoffrey Bourne.
Professor David Campbell.
Dr. J. N. Cruickshank.
Professor Stanley Davidson.

Dr. H. Gardiner-Hill.
Dr. T. L. Hardy.
Dr. S. I. Turkington.

Election of Ordinary Members

George James Aitken, M.B., F.R.F.P.S., Assistant Physician, Royal Infirmary, Glasgow.

Charles Gaffney Baker, O.B.E., M.D., F.R.C.P., Assistant Physician, Guy's Hospital.

William Arthur Bourne, M.D., F.R.C.P., Physician, Brighton General Hospital.

Wallace William Brigden, M.B., M.R.C.P., Assistant Physician, London Hospital.

Kenneth William Donald, M.D., M.R.C.P., Reader in Medicine, University of Birmingham.

William Herbert Hargreaves, O.B.E., F.R.C.P., Officer in Charge, Medical Division, The Queen Alexandra Military Hospital, London.

Mark Ian Alastair Hunter, M.D., F.R.C.P., Assistant Physician, St. George's Hospital.

Martin Cyril Gordon Israëls, M.D., F.R.C.P., Assistant Director, Department of Haematology, Royal Infirmary, Manchester.

Ranald Malcolm Murray-Lyon, M.D., F.R.C.P., Assistant Physician, Royal Infirmary, Edinburgh.

Alexander Slessor, M.B., F.R.F.P.S., Lecturer in Materia Medica and Therapeutics, University of Glasgow.

John Fisher Stokes, M.D., F.R.C.P., Assistant Physician, University College Hospital.

Reginald Norman Tattersall, O.B.E., M.D., F.R.C.P., Assistant Physician, Leeds General Infirmary.

The President then called on the Secretary to explain the recommendations of the Executive Committee which had been previously circulated to members. The Secretary reminded the Association that at the last Annual General Meeting it had been decided to form a special Sub-Committee with the terms of reference: 'To consider the future of the Association and to make recommendations'. On the invitation of the President a Sub-Committee had been set up under the chairmanship of Professor L. J. Witts, consisting of Dr. J. M. H. Campbell, Dr. T. C. Hunt, Professor R. Platt, Dr. E. E. Pochin, Sir Henry Tidy, and Dr. W. I. Card as Secretary. This special Sub-Committee had met and drawn up a report which had been considered at a special session of the Executive Committee. The Executive Committee had agreed with the findings of the special Committee, but suggested certain modifications for carrying them into effect. The main findings, and the recommendations of the Executive Committee, were in the hands of the Members. The Secretary asked permission to take the first part of the Report separately, so that this could then be discussed and a vote taken on the proposed amendments to the Rules.

The Secretary said that the section dealing with the size of the Association and possible methods for increasing facilities for membership had given rise to most difficulty. Both Committees had felt that the first consideration was to determine the proper size of the Association. At the moment this was about 350, consisting of 250 Ordinary Members, 80 to 90 Extra-Ordinary Members, a figure which was slowly rising, and some 12 Honorary Members. The total Membership might be expected to increase a little as the Association 'accumulated' Extra-Ordinary Members. If the policy of the Association was to continue to meet outside London, its size could not be indefinitely increased owing to difficulties of accommodation in some of the provincial centres. Both Committees felt strongly that meetings outside London should continue as in the past, and this decision, if accepted, automatically limited the size of the Association to one not very much larger than existed at present. Both Committees had equally felt that the facilities for entrance for younger physicians were inadequate, and that the average age of new Members was too high. For the last four years the Association had been able to admit an average of only 12 Members annually, whose average age was 38·5 years. All those who had served on the Executive Committee would agree on the great difficulty of making a selection and the unfortunate necessity of excluding many promising candidates. The problem the Association had to consider was therefore the difficult one of increasing facilities for new members while maintaining the total size of the Association at, or a little above, its present size. The Secretary said he believed that the Committee had considered all possible methods. Basically, however, the problem was quite simple; if the Association was to remain at a certain size, and if more Members were to come in at the younger end, then more Members must move out at the older end. There was no escape from this inevitable conclusion. The Committee therefore proposed a rule requiring resignation at the age of 65 on retirement from active hospital practice. They did not like making this suggestion, but it had been pointed out by Sir Henry Tidy that it was in fact a return to the original intention of the Association, and was implied in Rule 2.

The final unanimous recommendations of the Committee were:

1. That all Ordinary Members, with the exception of Original Members of the Association, should resign on reaching the age of 65.
2. That the total Ordinary Membership of the Association be limited to 350.
3. That Extra-Ordinary Membership be abolished, but that, for the first fifteen years of Membership only, a Member be required to attend one in three meetings as under Rule 20, but that after this period he be exempt.
4. That the vacancies so created for Membership be filled during the next two to three years at the discretion of the Executive Committee.

The effect of these recommendations was to increase slightly the size of the Association, to increase the facilities for Membership very considerably over the next two or three years, and thereafter to provide for a somewhat increased annual entry. The Committee felt that the hardship occasioned by retirement at 65 might be somewhat mitigated if they were allowed more latitude in election to Honorary Membership. The Secretary concluded by saying that the Committee must emphasize the fact that, without the introduction of a rule requiring resignation, there was no hope of permanently increasing facilities for Ordinary Membership of the Association, and they would especially appeal to those older Members, who had enjoyed or benefited by the Association in the past, to support this recommendation, so that more younger physicians might enjoy it in the future.

These recommendations aroused considerable discussion, in which Professors W. Melville Arnott, J. G. Scadding, and C. Bruce Perry, Drs. C. M. Fletcher, E. Bulmer, T. L. Hardy, and George Graham, Professor J. McMichael, Sir Philip Manson-Bahr, Professor R. Platt, Dr. Maurice Campbell, Professors F. J. Nattrass and L. J. Witts, Dr. Avery Jones, Sir John Parkinson, and others took part. Various suggestions were made to obviate the necessity for enforcing retirement at 65, but, as Professor Witts pointed out, these had all been previously considered by the special Sub-Committee.

An amendment to the Recommendations, proposed by Dr. Maurice Campbell and seconded by Professor Nattrass, that the new proposals be reconsidered in a year's time, was defeated, and the new amendments were put from the Chair:

'That, in Rule 2, the word "Extra-Ordinary" be deleted; that "250" be deleted and "350" inserted.

'That the paragraph "Extra-Ordinary Members.—Ordinary Members of not less than fifteen years' standing shall be eligible to apply for election as Extra-Ordinary Members on nomination by the Executive Committee. Such Members shall have the rights and privileges of Ordinary Members, but shall not be subject to Rule 20. The number of such Members elected annually shall not exceed eight" be deleted, and the following sentence be inserted: "All Ordinary Members, with the exception of Original Members of the Association, shall resign on reaching the age of 65."

'That, in Rule 20, the phrase "during the first fifteen years of Membership" be inserted after "Ordinary Member".'

These amendments were carried by 95 votes to 22.

The Secretary then spoke on the other points covered by the Report, in particular the relation of the Association to the specialist Societies. The Committee were aware of the vigorous growth of the specialist Societies and the loss thereby of papers to the Association. The possibility of a joint meeting with specialist Societies had been discussed in the past, and had again been ventilated. Apart from the possibility of a joint meeting with the Cardiac Society, the Committee did not think it was practicable. The view, however, had been put forward that symposia on suitable subjects might be of value, and that whereas a specialist Society viewed new work in its application to its own particular region, the Association, in representing the outlook of the general physician, might usefully consider the incorporation of new or special work into the pattern of medicine as a whole. This was something that by its very nature a specialist Society could not normally do. Such a symposium might replace the usual clinical demonstration that was held in the afternoons. On the value of the clinical demonstration the Executive Committee were divided, and asked for guidance from the Association.

There followed considerable discussion, and on a vote being taken there was very general agreement that symposia should be tried as an experiment for a period.

The Secretary then pointed out the difficulty of a new President taking office without having had the opportunity of attending the previous Committee meetings. The Committee had therefore recommended that the place of meeting should be decided two years in advance, and that the President-Elect be elected one year in advance. This necessitated the following amendments to the Rules, which were put from the Chair and carried:

'That, in Rules 3 and 4, the words "a President-Elect" be inserted after "President".'

The Secretary then said that, in view of the acceptance by the Association of the Executive Committee's recommendations, the Committee proposed for election the names of the following six additional Members:

Hector John Anderson, M.B., F.R.C.P., Physician to Out-patients, St. Thomas's Hospital.

Charles Allan Birch, M.D., F.R.C.P., Senior Physician, Chase Farm Hospital, Enfield.

Alexander Brown, M.D., F.R.C.P., Assistant Physician, Royal Infirmary, Glasgow.

Ronald Haxton Girdwood, M.B., F.R.C.P., Lecturer in Medicine, University of Edinburgh.

Henry Taylor Howat, M.B., F.R.C.P., Assistant Physician, Manchester Royal Infirmary.

Robert Brockie Hunter, M.B., F.R.C.P., Professor of Pharmacology and Therapeutics, University of St. Andrews.

Their formal election followed.

The Association then received a formal invitation from the Members from Sheffield to meet there in 1952 under the Presidency of Dr. Gurney Yates. This invitation was gratefully accepted.

The Chair was then taken by Professor Sir John McNee. He expressed the thanks of the Association to the retiring President, Sir John Parkinson.

SCIENTIFIC BUSINESS

Friday Morning, May 11

1. Dr. J. Innes reported some *Clinical Trials of Oral Nitrogen Mustards in Leukaemia and Allied Disorders*. He said that preparations of nitrogen mustard suitable for oral administration had been made available by Haddow and his fellow workers. Clinical trial of two such compounds, R.48 and R.151, had been in progress in Edinburgh since August 1948, and over 80 patients suffering from leukaemia and allied disorders had so far been treated. While no striking results were claimed, he said that there was evidence that some cases of chronic leukaemia and of reticulosis might show favourable responses over periods of many months and that treatment could be satisfactorily continued on an out-patient basis. The preliminary results obtained suggested that further study of these and related compounds was clearly indicated.

Professor L. J. Witts said that R.48 was also of value in some cases of polycythaemia vera.

Sir Lionel Whitby said that it was noticeable that the best results had been obtained in chronic lymphatic leukaemia in old subjects, in whom, in any case, the outlook was good. His own results in other types of leukaemia had been far from favourable.

Dr. Innes thought that urethane was the most hopeful drug. He agreed there should be considerable caution in assessing the results in elderly people.

2. Dr. Russell Brain discussed some *Factors in the Aetiology of Exophthalmic Ophthalmoplegia*. He reviewed the findings in 100 patients, of whom 43 were males and 57 were females. Males were thus affected more frequently than in exophthalmic goitre. Whereas 70 per cent. of females with exophthalmic goitre were under the age of 40, 81 per cent. of females with exophthalmic ophthalmoplegia were over that age. Five out of 69 patients with exophthalmic ophthalmoplegia had had between them seven relatives suffering from exophthalmic goitre. The previous endocrine history had been recorded in 69 cases; 23 of these patients had had previous thyrotoxicosis treated surgically or medically, and three had had myxoedema treated with thyroid extract. Dr. Brain suggested that exophthalmos was not due to thyrotoxicosis, and that though exophthalmic goitre and exophthalmic ophthalmoplegia were closely related aetiologically, exophthalmic ophthalmoplegia occurred in patients with a relatively inactive thyroid. He discussed the significance of the normal balance between pituitary and thyroid and its disturbance by thyrotoxicosis, by operations on the thyroid, and by previous thyroid treatment.

Dr. A. W. Spence pointed out some of the difficulties in accepting the theory that the production of exophthalmos was related to the level of thyrotrophin in the blood.

Dr. Russell Fraser thought that, while the aetiology remained obscure, Ophthalmic Graves' Disease might be a better term.

Dr. Russell Brain said that the anomalies that speakers had pointed out showed how little we knew about this disorder.

3. Dr. C. G. Baker, Mr. R. C. Brock (introduced), Dr. Maurice Campbell, and Dr. Paul Wood discussed the *Selection of Patients with Mitral Stenosis for Valvulotomy*. Dr. Maurice Campbell said that it was only a year since they had reported the good immediate result in six of the first eight patients submitted to mitral valvulotomy. They could now report the results in 50 patients after a longer period of observation. It was already clear that the young patient with orthopnoea and attacks of cardiac asthma or pulmonary oedema, often with haemoptysis, who was incapacitated but had not a very large heart, might be vastly improved by operation. The risk of this was not great, as all the eight deaths had occurred among the first 25 patients. Mitral regurgitation was not, as a rule, increased by a successful operation, and slight degrees of this or slight aortic stenosis or regurgitation did not prevent success, though in no patients who had been operated on were these thought to have been the predominant lesions. Calcification of the valve was often present, but gross calcification might prevent a good result. Auricular fibrillation, because it generally indicated a later stage of the disease, added greatly to the risk; six of the deaths had occurred in the 23 patients with fibrillation, and only two in the 27 who had had normal rhythm. They had noted great improvement in 35 of the 50 patients, and many of these, who could not work or walk far, could walk two miles or more and could resume their work after operation. There might be a considerable fall in the degree of pulmonary hypertension. More experience was needed about the degree of improvement that might be expected in the many varieties of this disease. When auricular fibrillation and congestive failure had been present for long, probably much could not be expected, but it was too early to say that these patients, too, might not get some benefit. The only certain contra-indication was the presence of active carditis. The risk of recurrent carditis had so far excluded all patients under 20 years of age.

Dr. R. W. D. Turner referred to an experience of nine cases which had been assessed in detail before operation. While he did not doubt the value of cardiac catheterization studies in order to gain further insight into the haemodynamics of mitral valvular disease, he did not think they were really necessary from the practical point of view. He had been impressed by the relative simplicity of the operation and its remarkable safety, and the smooth convalescence in suitable patients.

Dr. P. T. O'Farrell said that in the past few months at St. Vincent's Hospital six patients had been operated on for mitral stenosis. With one exception all had had auricular fibrillation. There were two deaths from post-operative complications, and in one patient the operation had had to be abandoned on account of dense calcification of the left auricle.

4. Dr. J. D. N. Nabarro, Dr. A. G. Spencer, and Dr. J. M. Stowers (introduced by Professor M. L. Rosenheim) reported the results of *Metabolic Balance Studies during Recovery from Severe Diabetic Ketosis*. Dr. Nabarro said that in the first 48 hours of treatment the patients retained extracellular fluid and electrolytes representing 20 per cent. of the normal body content. In this period there was a continuing excessive loss of water and electrolytes in the urine, closely related to the extent of the glycosuria. Cellular recovery might be described in three phases; water was taken up by the cells in the early hours of treatment; potassium, magnesium, and phosphorus were retained and largely restored during the next six to eight days, while re-synthesis of cell-protein was only apparent by the fourth to sixth day, and was not completed by the end of the period of study (12th day). Potassium supplements were shown to accelerate cellular restoration of this ion and to prevent the development of severe hypokalaemia, and they also appeared to correct or prevent the development of gastric dilatation, which was otherwise common in patients with diabetic acidosis.

Dr. G. Graham congratulated Dr. Nabarro on his excellent communication, and asked whether he had seen any symptoms due to hypokalaemia. He also suggested that it would be better to use Ringers' solution, which contained potassium, for any long-continued infusion, rather than normal saline. Dr. Nabarro, in reply, said that the muscular weakness and electrocardiographic changes associated with severe hypokalaemia were not seen in these patients. It was not safe to give parenteral solutions containing potassium at the start of treatment, as the plasma level might be high.

At 1 p.m. Members of the Association lunched in the Royal Faculty of Physicians and Surgeons, and afterwards attended a clinical demonstration of cases at the Western Infirmary. Members were entertained to tea by the Hospital Board of Management.

4.15 p.m. *Afternoon Session*

5. Dr. J. H. Kellgren, Dr. J. Bell, and Dr. G. K. Tutton (introduced) described the *Articular and other Connective Tissue Changes in Acromegaly*. Dr. Kellgren said that a study had been made of the clinical and radiological features of the joint changes associated with

acromegaly. In the more rapidly progressive cases the texture of the connective tissues became gelatinous, giving rise to abnormal mobility of the extremities. In these cases the spreading effect of hyaluronidase was decreased, and biopsy studies of skin, subcutis, and articular structures suggested that this change was associated with the deposition of much acellular collagen. He thought that this collagenization might result from the laying down of protein which was outside the general metabolic pool.

DR. J. B. GAYLOR noted that facial pain which had been observed in cases of acromegaly might be due to mal-occlusion of the teeth, and could be abolished by suitable orthodontic treatment.

6. DR. G. D. KERSLEY, DR. L. MANDEL, and DR. M. R. JEFFREY described the *Effect of Hypoglycaemia on Rheumatoid Arthritis*. They had given insulin in a dosage of 20 to 120 units in order to produce clinical hypoglycaemia and to stimulate the pituitary-adrenal complex. They had treated 72 patients in this way and observed a similar control series treated with hospitalization but without insulin. The striking features were, first, the immediate marked improvement of 45 per cent. of the treated patients compared with 13 per cent. of the controls, though in two months the majority of both groups relapsed; secondly, that the patients who responded to insulin and then relapsed had a much better response to ACTH than those that did not respond at all to insulin.

7. DR. G. M. WILSON (introduced by PROFESSOR E. J. WAYNE) described the *Local Circulatory Changes associated with the Development and Regression of Clubbing of the Fingers* in a series of cases. He showed that the blood-flow through clubbed fingers and toes was greater than that through normal digits under similar conditions. Reduction of this increased blood-flow, either by direct interference with the arterial supply or by successful treatment of the underlying disease, was followed by regression of the clubbing. The condition was apparently caused by an arterial inflow into the fingers in excess of physiological requirements.

8. DR. J. B. GAYLOR, DR. J. CAMPBELL, DR. H. ANDERSON, and DR. T. C. WHITE (introduced) spoke of varieties of facial pain. Dr. Gaylor said that the pain of tic douloureux was lancinating and confined to the distribution of the fifth cranial nerve. Paroxysmal pain was not pathognomic of trigeminal neuralgia, but occurred in disseminated sclerosis and in the syndrome of the temporo-mandibular joint. He pointed out that this joint had to undergo more adaptation than any other, because of loss of vertical dimension of the bite and overclosure of the jaw. When the temporo-mandibular ligament was torn under an anaesthetic or otherwise by overopening, the condyle of the mandible deformed the tympanic plate to give symptoms referable to the middle ear and to the territory of its primordial innervation. As a result the innervation of at least two of the branchial arches was disturbed, and gave the full picture of Costen's Syndrome (the syndrome of the temporo-mandibular joint).

DR. R. S. ALLISON inquired whether the speaker had come across any cases displaying this syndrome with unilateral flushing of the face and disturbance of sweating, of the kind seen in the so-called auriculotemporal syndrome.

The Members of the Association were entertained to sherry by the Glasgow Members in the University Club, and afterwards dined in the Bute Hall. The President, PROFESSOR SIR JOHN MCNEE, was in the Chair. The toast of the Association was proposed by the President, and that of the Guests by Professor David Campbell. Sir Hector Hetherington replied for the Guests, and the toast of the President was proposed by Professor Max Rosenheim.

Saturday, 9.30 a.m. *Morning Session*

9. DR. P. HUGH-JONES (introduced by DR. C. M. FLETCHER) described the *Assessment of Breathlessness by a Simple Standard Exercise Test*. He showed that the usual clinical step-test was unsatisfactory, because patients do an unknown and inconstant amount of exercise. These deficiencies in the test had been overcome by standardizing the exercise and measuring the minute-volume of expired air throughout the test. A nomogram was used to find the appropriate combination of step-height and rate so that all patients could be exercised at the rate of 350 kg.-m. of work per minute regardless of their weight. The ratio of ventilatory cost of exercise to the maximum ventilatory capacity could be regarded as a 'dyspnoeic index'. The results of using this standard exercise test on 162 subjects, representing men with five different radiological stages of pneumoconiosis and some normal subjects, all divided into three age-groups, were presented. They showed that breathlessness in pneumoconiosis was due to a reduction in maximum ventilation, measured independently, rather than to an increase in the ventilatory cost of exercise, except in those subjects who had complicating heart failure.

DR. K. W. DONALD thought that the correlation between subjective dyspnoea and an objective index was unsatisfactory in a number of cases of moderate or severe emphysema. Such patients might use well over half of their maximum breathing capacity and yet state quite emphatically that they were not short of breath. As pulmonary emphysema was so common, he thought this feature of the test was a disadvantage in its general application.

PROFESSOR J. MCMICHAEL congratulated the Cardiff workers on having found an objective test which correlated with the clinical history of dyspnoea. Some patients, however, could not complete the test, while others were not pushed to the limit of exercise-tolerance. In the former group could one really extrapolate from the figures obtained at 1½ minutes to get a hypothetical value for a five-minute test?

PROFESSOR W. M. ARNOTT emphasized the value of this communication. He pointed out that, in assessing the maximum breathing capacity, performance was influenced by the design of the recording apparatus (diameter of tubes, resonance-frequency of spirometer, &c.) so that, until there was widespread agreement on a standard pattern of apparatus, the first step in each laboratory was the construction of normal standards based on a reasonably large group.

DR. N. OSWALD said that it would seem that the degree of breathlessness would vary in such a test with the amount of sputum in the bronchial tree at the time of the test, and also with the time of year in which it was done. He asked whether the test had been performed before and after expectoration, and also at different times of year in the same patients.

DR. HUGH-JONES, in reply, said that, although any 'dyspnoeic index' using vital capacity to represent ventilatory reserve was not applicable in emphysema, he had not found any lack in the general agreement between clinical 'breathlessness' and the ratio of the ventilatory cost of standard exercise to the maximum breathing capacity. He thought that the method of expressing the test-results in patients who had failed to complete the five minutes of exercise was theoretically justifiable. It was true that the results for the voluntary maximum breathing capacity were influenced by the apparatus used, but the absolute values were not particularly important when the test results were used to measure the dyspnoeic ratio. Repeated exercise tests had been done in the same subjects on different days and at different times of day; spasm might well affect the results of the exercise test. He emphasized the fact that the results of the test had to be interpreted in the light of other information.

10. DR. P. C. REYNELL (introduced by PROFESSOR L. J. WITTS) spoke on the *Prognosis of Portal Hypertension*. He said that the syndrome of portal hypertension was believed to be due to an obstructive lesion in the course of the portal or splenic vein. A rise in portal venous pressure, with the development of collateral circulation, had been produced in rats by experimental hepatic cirrhosis and by constriction of the portal vein. In man, the clinical diagnosis of portal hypertension was usually made by the demonstration of oesophageal varices, and he had compared the prognosis of haemorrhage from varices in patients with and without liver damage. During the period under review all patients without evidence of liver damage had survived, but all except one of those with cirrhosis of the liver had died. He suggested that the prognosis of portal hypertension was determined mainly by the state of liver function.

THE PRESIDENT referred to the two types of portal obstruction, one within the liver (as in cirrhosis) and the other in association with thrombosis and tunnelling of the splenic vein first described by Warthin. The puzzle had always been to account for the lesion of the splenic vein, and this puzzle still remained.

DR. F. AVERY JONES thought that a portocaval anastomosis carried a mortality of about 20 per cent. The communication gave a much-needed picture of the prognosis of patients with portal hypertension in the younger age groups in whom operation might be considered.

PROFESSOR J. MCMICHAEL said that all agreed that the prognosis of gastro-intestinal bleeding in these cases was difficult. He asked how, in the group of 'liver damage', this was assessed. In the larger group with a good prognosis there must have been a number of patients with liver cirrhosis, but he presumed the disease was judged to be quiescent. It might be possible in the future, he thought, to get an approximate measure of portal pressure by occlusive catheterization of hepatic veins.

DR. T. E. GUMPERT asked what proportion of the patients described had had ascites.

DR. C. L. COPE asked about the effect of the sclerosis of veins on haemorrhage.

DR. REYNELL, in reply, said that in some cases portal- or splenic-vein thrombosis appeared to follow intra-abdominal infection or abdominal trauma, but in most cases the

aetiology was obscure. Ascites had not been seen in patients with extrahepatic portal obstructions; in those with cirrhosis of the liver it had occurred as a transient phenomenon after haemorrhage, or as a terminal event. Of the liver function tests used in distinguishing intrahepatic from extrahepatic obstructions, the flocculation tests and plasma-protein changes were the most useful. Gastric erosions and hypoprothrombinaemia might sometimes lead to gastrointestinal haemorrhage in patients with cirrhosis of the liver; the bleeding could not be assumed to be due to portal hypertension unless varices could be demonstrated. He had the impression that repeated injection of the varices with sclerosing fluids reduced the incidence of haemorrhage, but the question could not be answered decisively without a longer follow-up.

11. Dr. Douglas Hubble discussed the *Clinical Picture of Hypopituitarism, Genetic and Acquired*. He described six examples of the condition:

1. Pituitary dwarfism in a child, with pituitary hypogonadism in his first cousin.
2. Two cases of anorexia nervosa with absent gonadotrophins.
3. Growth-arrest in a child, associated with emotional anorexia.
4. Two cases of post-partum necrosis—Sheehan's syndrome.
5. Destructive lesion of the anterior pituitary in a man.
6. Haemochromatosis, with deposit of haemosiderin in the basophil cells of the anterior pituitary.

He concluded that a genetic hypopituitarism had so far been shown only to affect the sex and growth hormones; that malnutrition affected primarily the sex and growth hormones; that emotional factors have so far been shown only to depress the formation of sex hormones; that in destructive lesions of the pituitary the sex hormones are immediately depressed, while clinical evidence of hypocorticism and hypothyroidism appeared gradually over many years; that the deposit of haemosiderin in the basophil cells in haemochromatosis affected only the sex hormones.

The communication was discussed by Dr. D. A. K. Black and Dr. Russell Fraser.

12. Dr. A. Rae Gilchrist and Dr. John Tulloch (introduced) described the *Use of Tromexan in Coronary Thrombosis*. They said that the immediate prognosis in coronary thrombosis had been improved by administration of anti-coagulant drugs during the first four weeks after the onset. Tromexan, a dicoumarol derivative, was the most suitable drug at present available for use over a four-week period. In a series of 65 patients with coronary thrombosis admitted to the Royal Infirmary, Edinburgh, the mortality-rate in the first six weeks was 19·2 per cent., and the incidence of thrombo-embolic complications 4·6 per cent. No patient with such a complication died. Of the 12 deaths, four had occurred within three days of the onset; five of the remainder had been due to heart failure, two had been sudden and unexpected, and one had been due to a pontine haemorrhage.

Dr. A. A. F. Peel asked whether any attempt had been made to select cases suitable for anti-coagulants. In view of the frequency of coronary thrombosis and the nature of anti-coagulant treatment, which necessitates hospitalization and frequent laboratory tests, it was clearly desirable to find some means of selecting those patients for whom anti-coagulants were essential.

Dr. W. Phillips said that his experience in Cardiff had been in accord with that described in the communication, and he particularly emphasized the variability from day to day of the patient's response to tromexan. It was, as yet, uncertain whether anti-coagulant action needed to be completely uninterrupted and uniform to produce its optimum clinical effect, but if this was so it might be that prothrombin-time estimations should be made twice and not once daily, despite the difficulties of this demand on laboratory services.

Dr. Tulloch said in reply that (1) there was no means of selecting the cases that would exhibit thrombo-embolic complications, but if the Waugh-Ruddick heparin-retarded-clotting test were done daily, the time at which anti-coagulant therapy became essential could be determined, and the few cases not requiring anti-coagulants could probably be selected; (2) prothrombin-time measurements once daily were probably adequate; spreading the dose of tromexan over the day, and crushing the tablets, might help in overcoming fluctuation in response to the drug from day to day.

13. Dr. H. Conway (introduced by Professor Sir John McNee) discussed the *Aetiological Importance of Occult Idiopathic Steatorrhoea in Megaloblastic Anaemia of Young Adults*. He said that seven patients, who had been diagnosed between 1937 and 1949 as suffering from Addisonian pernicious anaemia when under the age of 30 and had been subsequently treated with parenteral liver, had been reinvestigated during 1950. The diagnosis had been confirmed in three patients, but four had been found to be suffering from steator-

rhoea, although bowel symptoms had never been prominent. Three of the latter group had responded inadequately to parenteral liver initially, and had still had refractory macrocytic anaemia ten, six, and five years later; the marrow was megaloblastic in one, and of an intermediate erythroblastic type in two. The remaining patient with steatorrhoea was not anaemic after three years' treatment, but the red cells were macrocytic. Presumptive evidence of the existence of steatorrhoea was provided by abnormal skin pigmentation, clubbing of digits, flat glucose-tolerance curves, and radiological 'deficiency patterns' of the small bowel; the final proof had been the demonstration of defective fat-absorption. No evidence of deficiency of the fat-soluble vitamins had been found. The patients who had been refractory to liver obtained great haematological and nutritional benefit from folic acid.

14. Dr. J. H. Hutchison described *Chronic Acidiosis in Infants due to Renal Tubular Deficiency, and its Association with Metastatic Calcification*. He said that this syndrome had occasionally been reported in British and American literature, and was characterized by anorexia, severe constipation, failure to thrive, chronic dehydration, a tendency to pass an alkaline urine, acidosis, and hyperchloraemia. In the fatal cases there had been a renal medullary calcinosis. Five infants suffering from this condition had been studied in detail. Three of these infants had responded to treatment with alkali, and chemical studies had produced evidence to show that the cause of the acidosis was an inability of the proximal renal tubules to reabsorb bicarbonate from the glomerular filtrate. Two patients had died. In one, autopsy had revealed nephrocalcinosis. In the other nephrocalcinosis had been absent, but there had been marked metastatic calcification affecting the lungs, endocardium, and coronary vessels. The kidney sections had revealed thickening of the basement membrane and underdevelopment of the proximal convoluted tubules; the glomeruli had been normal. He thought that metastatic calcification due to a pure tubular deficiency without glomerular damage had not previously been described.

Dr. B. E. Schlesinger said he had seen several cases of renal acidosis in infants, and thought that spontaneous recovery frequently took place. He had not seen metastatic calcification apart from nephrocalcinosis.

Dr. G. A. Smart asked whether there had been any episodes of muscular weakness due to low serum-potassium levels.

Dr. Hutchison, in reply, said that in one of his patients the alkali had recently been stopped and recovery seemed to have taken place. Hyperkaluria with hypokalaemia and muscular weakness had been reported in a similar condition in adults, but this had not been observed in his patients, who had had normal serum-potassium levels.

15. Dr. Douglas McAlpine and Dr. N. D. Compston (introduced) described *Some Factors which may Influence the Onset and Course of Disseminated Sclerosis*. Dr. McAlpine said that the disease had a small but significant familial incidence. An allergic history appeared to be more frequent than in a control population. Factors which might precipitate the onset or relapses were trauma (including operations), infections, and emotional upsets. In a minority of cases no precipitating factor could be determined. He said that pregnancy did not appear to influence the onset of the disease, and was much less important as a cause of relapses than had been formerly thought. Established symptoms might be temporarily affected by a variety of exogenous and endogenous factors. The geographical and occasional focal occurrence of the disease was as yet unexplained. The view that disseminated sclerosis was primarily due to a sensitization of the nervous system was on the whole supported by the occasional familial incidence, by the frequency of an allergic background, and by the nature of the precipitating factors.

Dr. E. G. L. Bywaters pointed out the difficulties of history-taking, and thought that the frequency of events preceding onset in the control and in the disseminated sclerosis groups could be usefully compared only if precautions were taken to 'pair' controls, and to inquire into the history over the same period of months from the present time as in the disease group.

Dr. R. S. Allison referred to a survey being conducted in Northern Ireland in order to find the incidence and distribution of cases. So far they had records of some 500 patients which seemed to confirm the belief, long held locally, that the disease was unduly prevalent in that area. There was evidence that the disease was more prevalent in certain areas than in others, and a relatively great familial incidence had been noted.

Professor Robert Platt said that some of the genealogical data shown by Dr. McAlpine suggested a dominant heredity (presumably with incomplete penetrance), since the disease had been shown to occur in three successive generations, and the numbers of cases in

parents and in siblings were approximately equal. He suggested that a blood-group study of disseminated sclerosis would be interesting, as he understood that nine human chromosomes were now labelled by blood-groups. Evidence of linkage would confirm a hereditary factor in disseminated sclerosis, and heredity might also explain the geographical distribution of the disease.

Dr. A. M. G. Campbell said that the traumatic factor in disseminated sclerosis was extremely difficult to assess. The familial incidence of the disease in the south-western area was in agreement with Dr. McAlpine's experience, being about 5 per cent., and there were also foci where the disease appeared to be unusually common in country districts. The rarity of the disease in South Africa had never been satisfactorily explained.

Dr. McAlpine, in reply, agreed with Dr. Bywaters on the difficulty of history-taking. He said that blood-group studies were already being undertaken.

16. Dr. G. T. Thomas and Dr. E. M. M. Besterman (introduced by Dr. E. G. L. Bywaters) described the *Clinical and Electrocardiographic Findings in Rheumatic Pericardial Effusions, and their Correlation with X-ray Changes.* Dr. Thomas said that in this series of 17 cases raised venous pressure, signs at the lung bases, and abnormal cardiac dullness were the most frequent clinical signs encountered. The first two of these were early signs, and in three cases had preceded X-ray evidence of effusions. The well-known signs at the lung bases were most often due to accompanying pleural effusions. The electrocardiogram had been abnormal in ten cases, normal in six, and doubtful in one. In four cases the electrocardiographic changes had been only transitory; in five they did not appear until some time after the onset of the effusions. Four of the six cases with normal tracings had had digitalis; the changes from pericarditis might have been masked by a digitalis effect.

The communication was discussed by Dr. C. M. Fletcher.

After lunch at the University Union, Members took part in excursions on the Clyde and to the Trossachs.

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